# Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD)

## Review information

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# Abstract

## Background

Attention deficit hyperactivity disorder (ADHD) is one of the most commonly diagnosed and treated psychiatric disorders in childhood. Typically, children with ADHD find it difficult to pay attention, they are hyperactive and impulsive.

Methylphenidate is the drug most often prescribed to treat children and adolescents with ADHD but, despite its widespread use, this is the first comprehensive systematic review of its benefits and harms.

## Objectives

To assess the beneficial and harmful effects of methylphenidate for children and adolescents with ADHD.

## Search methods

In February 2015 we searched six databases (CENTRAL, Ovid MEDLINE, EMBASE, CINAHL, PsycINFO, Conference Proceedings Citations Index), and two trials registers. We checked for additional trials in the reference lists of relevant reviews and included trials. We contacted the pharmaceutical companies that manufacture methylphenidate to request published and unpublished data.

## Selection criteria

We included all randomised controlled trials (RCTs) comparing methylphenidate versus placebo or no intervention in children and adolescents aged 18 years and younger with a diagnosis of ADHD. At least 75% of participants needed to have an intellectual quotient of at least 70 (i.e. normal intellectual functioning). Outcomes assessed included ADHD symptoms, serious adverse events, non-serious adverse events, general behaviour and quality of life.

## Data collection and analysis

Seventeen review authors participated in data extraction and risk of bias assessment, and two review authors independently performed all tasks. We used standard methodological procedures expected within Cochrane. Data from parallel-group trials and first period data from cross-over trials formed the basis of our primary analyses; separate analyses were undertaken using post-cross-over data from cross-over trials. We used Trial Sequential Analyses to control for type I (5%) and type II (20%) errors, and we assessed and downgraded evidence according to the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach for high risk of bias, imprecision, indirectness, heterogeneity and publication bias.

## Main results

*The studies.* We included 38 parallel-group trials (5111 participants randomised) and 147 cross-over trials (7134 participants randomised). Participants included individuals of both sexes, at a boys-to-girls ratio of 5:1, and participants' ages ranged from 3 to 18 years across most studies (in two studies ages ranged from 3 to 21 years). The average age across all studies was 9.7 years. Most participants were from high-income countries.

The duration of methylphenidate treatment ranged from 1 to 425 days, with an average duration of 75 days. Methylphenidate was compared to placebo (175 trials) or no intervention (10 trials).

*Risk of Bias.* All 185 trials were assessed to be at high risk of bias.

*Primary outcomes.* Methylphenidate may improve teacher-rated ADHD symptoms (standardised mean difference (SMD) -0.77, 95% confidence interval (CI) -0.90 to -0.64; 19 trials, 1698 participants; very low-quality evidence). This corresponds to a mean difference (MD) of -9.6 points (95% CI -13.75 to -6.38) on the ADHD Rating Scale (ADHD-RS; range 0 to 72 points; DuPaul 1991a). A change of 6.6 points on the ADHD-RS is considered clinically to represent the minimal relevant difference. There was no evidence that methylphenidate was associated with an increase in serious (e.g. life threatening) adverse events (risk ratio (RR) 0.98, 95% CI 0.44 to 2.22; 9 trials, 1532 participants; very low-quality evidence). The Trial Sequential Analysis-adjusted intervention effect was RR 0.91 (CI 0.02 to 33.2).

*Secondary outcomes.* Among those prescribed methylphenidate, 526 per 1000 (range 448 to 615) experienced non-serious adverse events, compared with 408 per 1000 in the control group. This equates to a 29% increase in the overall risk of any non-serious adverse events (RR 1.29, 95% CI 1.10 to 1.51; 21 trials, 3132 participants; very low-quality evidence). The Trial Sequential Analysis-adjusted intervention effect was RR 1.29 (CI 1.06 to 1.56). The most common non-serious adverse events were sleep problems and decreased appetite. Children in the methylphenidate group were at 60% greater risk for trouble sleeping/sleep problems (RR 1.60, 95% CI 1.15 to 2.23; 13 trials, 2416 participants), and 266% greater risk for decreased appetite (RR 3.66, 95% CI 2.56 to 5.23; 16 trials, 2962 participants) than children in the control group.

Teacher-rated general behaviour seemed to improve with methylphenidate (SMD -0.87, 95% CI -1.04 to -0.71; 5 trials, 668 participants; very low-quality evidence).

A change of seven points on the Child Health Questionnaire (CHQ; range 0 to 100 points; Landgraf 1998) has been deemed a minimal clinically relevant difference. The change reported in a meta-analysis of three trials corresponds to a MD of 8.0 points (95% CI 5.49 to 10.46) on the CHQ, which suggests that methylphenidate may improve parent-reported quality of life (SMD 0.61, 95% CI 0.42 to 0.80; 3 trials, 514 participants; very low-quality evidence).

## Authors' conclusions

The results of meta-analyses suggest that methylphenidate may improve teacher-reported ADHD symptoms, teacher-reported general behaviour, and parent-reported quality of life among children and adolescents diagnosed with ADHD. However, the low quality of the underpinning evidence means that we cannot be certain of the magnitude of the effects.

Within the short follow-up periods typical of the included trials, there is some evidence that methylphenidate is associated with increased risk of non-serious adverse events, such as sleep problems and decreased appetite, but no evidence that it increases risk of serious adverse events.

Better designed trials are needed to assess the benefits of methylphenidate. Given the frequency of non-serious adverse events associated with methylphenidate, the particular difficulties for blinding of participants and outcome assessors point to the advantage of large, 'nocebo tablet' controlled trials. These use a placebo-like substance that causes adverse events in the control arm that are comparable to those associated with methylphenidate. However, for ethical reasons, such trials should first be conducted with adults, who can give their informed consent.

Future trials should publish depersonalised individual participant data and report all outcomes, including adverse events. This will enable researchers conducting systematic reviews to assess differences between intervention effects according to age, sex, comorbidity, type of ADHD and dose. Finally, the findings highlight the urgent need for large RCTs of non-pharmacological treatments.

# Plain language summary

## Benefits and harms of methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD)

### Review question

We reviewed the evidence of the effects of methylphenidate on the behaviour of children and adolescents with ADHD.

### Background

ADHD is one of the most commonly diagnosed and treated childhood psychiatric disorders. Children diagnosed with ADHD find it hard to concentrate. They are often hyperactive (fidgety, unable to sit still for long periods) and impulsive (doing things without stopping to think). ADHD can make it difficult for children to do well at school, because they find it hard to follow instructions and to concentrate. Their behavioural problems can interfere with their ability to get on well with family and friends, and they often get into more trouble than other children. Methylphenidate is the drug most often prescribed to treat children and adolescents with ADHD.

### Study characteristics

We found 185 randomised controlled trials (RCTs; studies in which participants are randomly assigned to one of two or more treatment groups), involving 12,245 children or adolescents with a diagnosis of ADHD. Most of the trials compared methylphenidate to a placebo – something designed to look and taste the same as methylphenidate but with no active ingredient. Most trials were small and of low quality. Treatment generally lasted an average of 75 days (range 1 to 425 days), making it impossible to assess the long-term effects of methylphenidate. Seventy-two of the 185 included trials (40%) were funded by industry.

The evidence is current to February 2015.

### Key results

Findings suggest that methylphenidate might improve some of the core symptoms of ADHD – reducing hyperactivity and impulsivity, and helping children to concentrate. Methylphenidate might also help to improve the general behaviour and quality of life of children with ADHD. However, we cannot be confident that the results accurately reflect the size of the benefit of methylphenidate.

The evidence in this review of RCTs suggests that methylphenidate does not increase the risk of serious (life threatening) harms when used for periods of up to six months. However, taking methylphenidate is associated with an increased risk of non-serious harms such as sleeping problems and decreased appetite.

### Quality of the evidence

The quality of the evidence was very low for all outcomes. It was possible for people in the trials to know which treatment the children were taking, the reporting of the results was not complete in many trials and for some outcomes the results varied across trials. These considerations limit our confidence in the overall results of the review.

### Conclusions

At the moment, the quality of the available evidence means that we cannot say for sure whether taking methylphenidate will improve the lives of children and adolescents with ADHD. Methylphenidiate is associated with a number of non-serious adverse events such as problems with sleeping and decreased appetite. Although we did not find evidence that there is an increased risk of serious adverse events, we need trials with longer follow-up to better assess the risk of serious adverse events in people who take methylphenidate over a long period of time.

Given that methylphenidate is associated with adverse events, designing high quality trials is challenging. It can be easy for clinicians, researchers and participants to work out whether a child is in the experimental group (receiving methylphenidate) or in the control group (receiving the placebo). This is a serious risk of bias that can make us less confident in the results of a trial. One way to avoid this is to design trials that compare methylphenidate with a placebo that can produce similar adverse events, but which has no other active ingredient. These trials are known as 'nocebo trials'. For ethical reasons, nocebo trials should first be undertaken with adults. Only if the results suggest that methylphenidate is effective for adults, should researchers consider recruiting children to trials with this design.

# Background

## Description of the condition

Attention deficit hyperactivity disorder (ADHD) is one of the most commonly diagnosed and treated childhood psychiatric disorders (Scahill 2000). The prevalence of ADHD in children and adolescents is estimated to be 3% to 5% (Polanczyk 2007 ), depending on the classification system used, with boys two to four times more likely to be diagnosed than girls (Schmidt 2009). Individuals with ADHD exhibit difficulty with attentional and cognitive functions such as solving problems, planning, orienting, maintaining flexibility, sustaining attention, inhibiting response and sustaining a working memory (Pasini 2007; Sergeant 2003). They also have difficulty handling affective features such as motivational delay and mood dysregulation ( Castellanos 2006; Nigg 2005; Schmidt 2009).

Diagnosis of ADHD is confirmed through recognition of excessive inattention, hyperactivity and impulsivity in a child, before 12 years of age, that impair his or her functioning or development (APA 2013; WHO 1992). This diagnosis may be based on 18 symptoms indicative of inattention, hyperactivity and impulsivity, according to the principal diagnostic classification systems - *International Classification of Diseases, 10th Revision* (ICD-10; WHO 1992), and the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5; APA 2013). The criteria of the ICD-10 and the DSM–5 require that inattention, hyperactivity and impulsivity are pervasive, that is, are seen in a range of situations for at least six months and are present before the age of six (ICD-10; WHO 1992) or 12 years (DSM-5; APA 2013), and that some impairment resulting from these symptoms is observed in two or more settings. Clinically significant impairment in social, academic or occupational functioning must also be evident (APA 1994; APA 2000; APA 2013; WHO 1992). The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV; APA 1994), provides three different subtypes to identify and classify particular symptoms, namely 'predominantly inattentive type', 'predominantly hyperactive-impulsive type' or 'combined type', the last of which presents with both hyperactive-impulsive and inattentive symptoms (Willcut 2012).

ADHD is seen increasingly as a developmental psychiatric disorder that extends into adulthood and occurs with high heterogeneity and comorbidity with other psychiatric disorders (Schmidt 2009). Comorbid disorders are common in ADHD. The Multimodal Treatment of Attention Deficit Hyperactivity Disorder (MTA) trial identified one or more comorbid disorders in almost 40% of participants (MTA 1999). These included oppositional defiant disorder, conduct disorder, depression, anxiety, tics, learning difficulties and cognitive deficits (Jensen 2001; Kadesjö 2001).

Rising rates of ADHD diagnosis, possible harm to children resulting from drug treatment (Zito 2000), and variation in prevalence estimates are matters of increasing concern (Moffit 2007; Polanczyk 2014). The need for a validated diagnostic test to confirm the clinical diagnosis of ADHD has given rise to debate about its validity as a diagnosis (Timimi 2004). Professional and national bodies have developed guidelines on assessment, diagnosis and treatment of ADHD in an attempt to ensure that high standards are maintained in diagnostic and therapeutic practice (American Academy of Pediatrics 2011; CADDRA 2011; NICE 2009; Pliszka 2007a; SIGN 2009). Psychosocial interventions, such as parent management training, are recommended in the first instance for younger children and for those with mild to moderate symptoms (American Academy of Pediatrics 2011; NICE 2009; Pliszka 2007a), and stimulants (given alone or in combination with psychosocial interventions) are recommended for children with more severe ADHD (American Academy of Pediatrics 2011; CADDRA 2011; NICE 2009).

## Description of the intervention

Methylphenidate, dexamphetamine and atomoxetine (a non-stimulant selective noradrenaline reuptake inhibitor) are recommended medical treatments for children and adolescents with ADHD (Greenhill 2006b; NICE 2009). Globally, methylphenidate, the drug of choice, has been used for longer than 50 years for the treatment of children with ADHD ( Kadesjö 2002; NICE 2009). Research suggests that the combination of behavioural therapy (e.g. behavioural parent training, school consultation, direct contingency management) and pharmacotherapy might benefit children with ADHD (Gilmore 2001 ; MTA 1999).

Methylphenidate is approved for the treatment of individuals with ADHD and narcolepsy (Kanjwal 2012). Pharmacological treatment of children and adolescents with ADHD is reported to have a beneficial effect on the major symptoms of hyperactivity, impulsivity and inattention. The dosage of the intervention can vary significantly between children, with some responding to relatively low dosages and others requiring larger doses to achieve the same effect (Stevenson 1989). Therefore, it is important that the dose of methylphenidate is titrated to an optimal level that maximises therapeutic benefits while producing minimal adverse events. The dose can range from 5 mg to 60 mg methylphenidate administered two to three times daily (Pliszka 2007a). Furthermore, treatment with methylphenidate should not be provided without pause. Medication-free periods are recommended to reassess effects of treatment on symptoms (Kidd 2000; NICE 2009).

## How the intervention might work

It is presumed that the effects of methylphenidate on ADHD symptoms are related to its effects on dopaminergic and noradrenergic neurotransmissions within the central nervous system (CNS) (Engert 2008). Methylphenidate acts by inhibiting catecholamine reuptake, primarily as a dopamine-norepinephrine reuptake inhibitor, modulating levels of dopamine and to a lesser extent levels of norepinephrine. Methylphenidate binds to and blocks dopamine and norepinephrine transporters (Heal 2006; Iversen 2006), and increased concentrations of dopamine and norepinephrine in the synaptic cleft lead to escalated neurotransmission.

The bioavailability of oral methylphenidate is 11% to 52%. Instant-release methylphenidate has a duration of action of around 2 to 4 hours, and sustained-release and extended-release formulations of methylphenidate have a duration of action of 3 to 8 hours and 8 to 12 hours, respectively (Kimko 1999). Methylphenidate is thought to activate self regulated control processes

to ameliorate what are believed to be the core neurofunctional problems of ADHD (Barkley 1977a; Schulz 2012; Solanto 1998). Evidence suggests that symptom control is strongly related to functional improvement (Biederman 2003b; Cox 2004a ; Swanson 2004a).

Studies indicate that methylphenidate is effective for treating both the core symptoms of ADHD (inattention, hyperactivity and impulsivity), and aggression (Connor 2002), with the result that children can manage their impulsivity better (Barkley 1981; Barkley 1989a; Shaw 2012). However, a child or adolescent may become less responsive to methylphenidate. In a supplementary analysis of the trial 'A Comparison of Methylphenidates in an Analog Classroom Setting' (COMACS), investigators found that girls had a superior response to methylphenidate (Sonuga-Barke 2007; Swanson 2004a). In addition, Barkley 1991b noted differences in response to methylphenidate between ADHD inattentive and combined subtypes: children with the inattentive subtype were judged to have a less favourable response to methylphenidate than those diagnosed with the combined subtype. Furthermore, debate continues regarding whether it is valid to diagnose pre-school children with ADHD, and whether methylphenidate is efficacious and safe for use by pre-school children with ADHD ( Greenhill 2006b).

### Why it is important to do this review

Over the past 15 years, several published systematic reviews have investigated the efficacy of methylphenidate for ADHD (with or without meta-analysis). Fifteen reviews have pooled results on methylphenidate treatment for children and adolescents with ADHD (Bloch 2009; Charach 2011; Charach 2013; Faraone 2002; Faraone 2006; Faraone 2009; Faraone 2010; Hanwella 2011; Kambeitz 2014; King 2006; Maia 2014; Punja 2013; Reichow 2013; Schachter 2001; Van der Oord 2008). However, none of these were conducted as Cochrane systematic reviews, thus most (Bloch 2009; Charach 2011; Charach 2013; Faraone 2002; Faraone 2006; Faraone 2009; Faraone 2010; Kambeitz 2014; King 2006; Schachter 2001; Van der Oord 2008) did not adhere to the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* ( Higgins 2011) nor to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines ( Liberati 2009; Moher 2015), and for none of these reviews was a peer-reviewed protocol published before the analyses were conducted. Thirteen did not undertake subgroup analyses examining the effects of comorbidity on treatment effects (Bloch 2009; Charach 2011; Charach 2013; Faraone 2002; Faraone 2006; Faraone 2009; Faraone 2010; Hanwella 2011; Kambeitz 2014; Maia 2014; Punja 2013; Schachter 2001; Van der Oord 2008); some did not control for treatment effects by ADHD subtype (Bloch 2009; Charach 2013; Faraone 2002; Hanwella 2011; Kambeitz 2014; King 2006; Maia 2014; Punja 2013; Schachter 2001; Van der Oord 2008); and others did not consider effects according to dose of methylphenidate (Charach 2011; Charach 2013; Faraone 2006; Faraone 2009; Hanwella 2011; Kambeitz 2014; Maia 2014; Punja 2013; Reichow 2013; Van der Oord 2008). In addition, as regards the outcomes, most meta-analyses pooled data from parents, teachers and independent assessors (Bloch 2009; Charach 2011; Charach 2013; Hanwella 2011; Kambeitz 2014; King 2006; Reichow 2013), and did not separate outcome measures for inattention and hyperactivity/impulsivity (Bloch 2009; Charach 2013; Faraone 2002; Faraone 2006; Faraone 2009; Hanwella 2011; Kambeitz 2014; Van der Oord 2008). Moreover, most previous reviews investigated only the effects of methylphenidate on symptoms of ADHD; review authors did not present data on spontaneous adverse events (Charach 2013; Faraone 2002; Faraone 2006; Faraone 2009; Faraone 2010; Hanwella 2011; Kambeitz 2014; Maia 2014; Van der Oord 2008), nor on adverse events as measured by rating scales (Bloch 2009; Charach 2013; Faraone 2002; Faraone 2006; Faraone 2009; Faraone 2010; Hanwella 2011; Kambeitz 2014; King 2006; Maia 2014; Punja 2013; Reichow 2013; Schachter 2001; Van der Oord 2008), and they did not try to explain why such information was not provided. Finally, these reviews did not systematically assess risk of random errors, risk of bias and trial quality (Bloch 2009; Charach 2011; Charach 2013; Faraone 2002; Faraone 2006; Faraone 2009; Faraone 2010; Hanwella 2011; Kambeitz 2014; King 2006; Van der Oord 2008). These shortcomings plus other methodological limitations, including potential bias in excluding non-English publications (Charach 2013; Faraone 2010; Punja 2013; Van der Oord 2008), and in not searching the principal major international databases nor reporting search terms clearly (Bloch 2009; Faraone 2002; Kambeitz 2014; Reichow 2013), may have compromised data collection, consequently calling the results of these previous meta-analyses into question.

Given mounting concerns regarding increasing use of methylphenidate in children younger than six years of age, it is vital that researchers explore risk versus benefit of treatment in this younger population (US FDA 2011). Although stimulant medications may have a favourable risk-benefit profile, they might carry potential risks of both serious and non-serious adverse events. Adverse events most often associated with methylphenidate include headache, sleep problems, tiredness and decreased appetite. Serious adverse reactions, such as psychotic symptoms and mood disorders, affect about 3% of children treated with methylphenidate (Block 1998; Cherland 1999; MTA 1999; NICE 2009; Pliszka 1998). Some studies indicate that methylphenidate can decrease children's height and weight (Schachar 1997b; Swanson 2004a; Swanson 2009). Other studies report sudden death though it remains unclear whether these deaths are directly related to methylphenidate treatment (Vitiello 2008); researchers are currently exploring the link between sudden death and treatment with methylphenidate (US FDA 2011).

Given the limitations of existing reviews, we conducted a systematic review of the benefits and harms of methylphenidate for children and adolescents with ADHD while adhering to the recommendations of The Cochrane Collaboration (Higgins 2011) and to PRISMA guidelines (Liberati 2009; Moher 2015).

This systematic review focuses on the beneficial and harmful effects of methylphenidate in randomised controlled trials and is the first of two systematic reviews. A second review focused on harms reported in non-randomised studies is under way ( Storebø in press).

## Objectives

To assess the beneficial and harmful effects of methylphenidate for children and adolescents with ADHD.

# Methods

## Criteria for considering studies for this review

### *Types of studies*

Randomised controlled trials (RCTs) of methylphenidate for the treatment of children and adolescents with ADHD. We included trials irrespective of language, publication year, publication type or publication status.

### *Types of participants*

Children and adolescents aged 18 years and younger with a diagnosis of ADHD, according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)*, Third Edition* (DSM-III; APA 1980), *Third Edition Revised* (DSM-III-R; APA 1987), *Fourth Edition* (DSM-IV; APA 1994), and *Fifth Edition* (DSM-5; APA 2013), or with a diagnosis of hyperkinetic disorders according to the *International Statistical Classification of Diseases and Related Health Problems, Ninth Revision* (ICD-9), and *10th Revision* (ICD-10; WHO 1992). We included participants with ADHD with or without comorbid conditions such as conduct or oppositional disorders, tics, depression, attachment disorders or anxiety disorders. Trials eligible for inclusion were those in which at least 75% of participants were aged 18 years or younger, and the mean age of the trial population was 18 years or younger. We also required that at least 75% of participants had a normal intellectual quotient (IQ > 70).

### *Types of interventions*

Methylphenidate, administered at any dosage or in any formulation as part of any medical treatment regimen, compared with placebo or with no intervention.

We permitted cointerventions if intervention groups received cointerventions similarly. Consequently, we did not permit polypharmacy as a cointervention in one of the groups.

### *Types of outcome measures*

#### Primary outcomes

1. ADHD symptoms (attention, hyperactivity and impulsivity), measured over the short term (within six months) and over the long term (longer than six months) by psychometric instruments or by observations of behaviour, using, for example, Conners' Teacher Rating Scales (Conners 1998a; Conners 2008). Raters could be teachers, independent assessors or parents. We chose to report the results of teacher-rated outcomes as primary outcomes (see Results).
2. Numbers of serious adverse events. We defined a serious adverse event as any event that led to death, was life-threatening, required in-patient hospitalisation or prolongation of existing hospitalisation or resulted in persistent or significant disability, or as any important medical event that may have jeopardised the patient's life or that required intervention for prevention. We considered all other adverse events as non-serious (ICH 1996).

#### Secondary outcomes

1. Non-serious adverse events. We assessed all adverse events, including, for example, growth retardation and cardiological, neurological and gastrointestinal events, as described in *ICH* (International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use) *Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R1)* (ICH 1996).
2. General behaviour in school and at home, as rated by psychometric instruments such as the Child Behaviour Checklist (CBCL; Achenbach 1991), measured over the short term (within six months) and over the long term (longer than six months). Raters could be teachers, independent assessors or parents. We chose to report the results of teacher-rated outcomes as primary outcomes (see Results).
3. Quality of life, as measured by psychometric instruments such as the Child Health Questionnaire (CHQ; Landgraf 1998). Raters could be teachers, independent assessors or parents.

## Search methods for identification of studies

### *Electronic searches*

We ran the first literature searches in October 2011 and updated them in November 2012, March 2014 and most recently between 26 February and 10 March 2015. We searched the following sources.

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 2; part of *The Cochrane Library*, which includes the Specialised Register of the Cochrane Developmental, Psychosocial and Learning Problems Group), searched 10 March 2015.
2. Ovid MEDLINE (1948 to current), searched 10 March 2015.
3. EMBASE (Ovid; 1980 to current), searched 10 March 2015.
4. CINAHL (Cumulative Index to Nursing and Allied Health Literature; EBSCOhost; 1980 to current), searched 10 March 2015.
5. PsycINFO (Ovid; 1806 to current), searched 10 March 2015.
6. Conference Proceedings Citation Index - Science (CPCI-S) and Conference Proceedings Citation Index - Social Science & Humanities (CPCI-SS&H) (Web of Science; 1990 to 17 March 2015), searched 19 March 2015.
7. ClinicalTrials.gov (1999 to current), searched 26 February 2015.
8. World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; who.int/ictrp/en; 1999 to current), searched 26 February 2015.

The search strategy for each database is shown in Appendix 1. We searched CENTRAL, Ovid MEDLINE, EMBASE and PsycINFO using two separate search strategies (one for efficacy of methylphenidate and one for adverse events of methylphenidate). For the remaining databases, we used one broad strategy to capture trials on efficacy and trials on adverse events. To overcome poor indexing and abstracting, we listed individual brand names within the search strategies. We did not limit searches by language, year of publication or type or status of publication. We sought translation of relevant sections of non-English language articles.

### *Searching other resources*

To find additional relevant trials not identified by electronic searches, we checked the bibliographic references of identified review articles, meta-analyses and a selection of included trials. Furthermore, we requested published and unpublished data from pharmaceutical companies manufacturing methylphenidate, including Shire, Medice (represented in Denmark by HB Pharma), Janssen-Cilag and Novartis (Appendix 2). We also requested data from unpublished trials from experts in the field.

## Data collection and analysis

We conducted this review according to the recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and performed analyses using Review Manager (RevMan), Version 5.3 - the statistical software of The Cochrane Collaboration (Review Manager 2014).

### *Selection of studies*

Eleven review authors (ER, FLM, HBK, KBR, MH, MS, OJS, TDN, SR, TK and TB) worked together in groups of two and independently screened titles and abstracts of all publications obtained from the literature searches; uncertainty or disagreements were resolved by consensus or by consultation with a third review author. We obtained full-text articles of trials presenting potentially relevant data and assessed them against our listed inclusion criteria. We discussed disagreements, and if agreement or consensus could not be reached, we consulted a third review author (OJS).

### *Data extraction and management*

Working together in groups of two, 17 review authors extracted data (CGr, CRMM, DGa, DGi, ER, ES, FLM, HK, KBR, MH, MJR, MS, MZ, OJS, RK, SR and TDN). We resolved disagreements by discussion and we used an arbiter if required. When data were incomplete, or when data provided in published trial reports were unclear, we contacted trial authors to ask for clarification of missing information. We contacted the authors of all cross-over trials to obtain first period data on ADHD symptoms.

We developed data extraction forms a priori (after performing data extraction pilots, we updated these forms to accommodate extraction of more detailed data and to facilitate standardised approaches to data extraction among review authors). These extraction forms were used by all data extractors (see Appendix 3; Appendix 4).

Six review authors (CRMM, FLM, MH, HK, ER and OJS) entered data into RevMan (Review Manager 2014).

### *Assessment of risk of bias in included studies*

For each included trial, data extractors independently evaluated risk of bias domains (listed below), resolving disagreements by discussion. For each domain, we assigned each trial to one of the following three categories: low risk of bias, unclear (uncertain) risk of bias or high risk of bias, according to guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Given the risk of overestimation of beneficial intervention effects and underestimation of harmful intervention effects in RCTs with unclear or inadequate methodological quality (Kjaergard 2001; Lundh 2012; Moher 1998; Savović 2012a; Savović 2012b; Schulz 1995; Wood 2008), we assessed the influence of risk of bias on our results (see Subgroup analysis and investigation of heterogeneity). Risk of bias components were as follows.

#### Random sequence generation

1. Low risk of bias. The method used was adequate (e.g. computer-generated random numbers, table of random numbers) or was unlikely to introduce selection bias.
2. Unclear risk of bias. Information was insufficient for assessment of whether the method used could introduce selection bias.
3. High risk of bias. The method used was likely to introduce bias.

#### Allocation concealment

1. Low risk of bias. The method used (e.g. central allocation) was unlikely to bias allocation to groups.
2. Unclear risk of bias. Information was insufficient for assessment of whether the method used could bias allocation to groups.
3. High risk of bias. The method used (e.g. open random allocation schedule) could bias allocation to groups.

#### Blinding of participants and personnel

1. Low risk of bias. The method of blinding was described sufficiently and blinding was conducted in a satisfactory way that was unlikely to introduce performance bias.
2. Unclear risk of bias. Information was insufficient for assessment of whether adequate blinding was used and whether it was likely to introduce performance bias.
3. High risk of bias. No blinding or incomplete blinding was described.

#### Blinding of outcome assessment

1. Low risk of bias. The method of blinding was described and blinding was conducted in a satisfactory way that was unlikely to introduce detection bias.
2. Unclear risk of bias. Information was insufficient for assessment of whether the type of blinding used was likely to bias the estimate of effect.
3. High risk of bias. No blinding or incomplete blinding was described.

#### Incomplete outcome data

1. Low risk of bias. Underlying reasons for missing data probably would not affect outcome measurement regarding effects of methylphenidate, as all missing data can be considered as missing at random or all data were reported.
2. Unclear risk of bias. Information was insufficient for assessment of whether missing data or the method used to handle missing data was likely to bias the estimate of effect.
3. High risk of bias. The crude estimate of effects could be biased given the reasons for the missing data.

#### Selective reporting

1. Low risk of bias. The trial protocol was available and all pre-specified outcomes of interest were reported.
2. Unclear risk of bias. Information was insufficient for assessment of whether selective outcome reporting could have occurred.
3. High risk of bias. Not all of the primary outcomes specified beforehand were reported or participants were excluded after randomisation (selection bias).

#### Vested interest bias

1. Low risk of bias. The trial was not funded by any parties that might be considered to have a conflict of interest (e.g. a manufacturer of methylphenidate).
2. Unclear risk of bias. The source of funding was not clear.
3. High risk of bias. The trial was funded by parties that might have had a conflict of interest (e.g. a manufacturer of methylphenidate) or potential conflicts of interest were reported by trial authors.

#### Other potential sources of bias

1. Low risk of bias. The trial appeared to be free of other sources of bias.
2. Unclear risk of bias. Information was inadequate for assessment of other possible sources of bias.
3. High risk of bias. Other sources of bias were identified.

Seven of the above domains are specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011 ). We added an eighth domain - vested interest (Storebø 2012). Andreas Lundh and colleagues have shown that there are many subtle mechanisms through which sponsorship and conflict of interest may influence intervention effects on outcomes. The AMSTAR (**A** **M**ea**S**urement **T**ool to **A**ssess systematic **R**eviews) tool for methodological quality assessment of systematic reviews also includes funding and conflicts of interest as a domain (amstar.ca). For more information, please see editorials by Bero 2013 and Sterne 2013, and the commentary by Gøtzsche 2015.

We defined low risk of bias trials as trials that had low risk of bias in all domains. We considered trials with one or more unclear or high risk of bias domains as trials with high risk of bias.

Some trials excluded methylphenidate non-responders, placebo responders and/or participants who had adverse events due to the medication. We did not consider these trials to be at risk of bias as participants were excluded before randomisation. However, to identify whether this 'cohort selection bias of all participants' had an effect on estimates of effectiveness, we conducted subgroup analyses based on these criteria (Subgroup analysis and investigation of heterogeneity).

### *Measures of treatment effect*

The treatment effect was defined as an improvement in ADHD symptoms, general behaviour and quality of life.

#### Dichotomous data

We summarised dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs). We calculated the risk difference (RD).

#### Continuous data

If the same measure of a given continuous outcome was used in all trials in a meta-analysis, we calculated mean differences (MDs) with 95% CIs. If different measures were used, we calculated standardised mean differences (SMDs) with 95% CIs. If trials did not report means and standard deviations but did report other values (e.g. *t*-tests, P values), we transformed these into standard deviations.

For primary analyses of teacher-rated ADHD symptoms, teacher-rated general behaviour and quality of life, we transformed SMDs into MDs on the following scales to assess whether results exceeded the minimum clinically important difference: ADHD Rating Scale (ADHD-RS; DuPaul 1991a), Conners' Global Index (CGI; Conners 1998a) and Child Health Questionnaire (CHQ; Landgraf 1998). We identified a minimal clinically relevant difference (MIREDIF) of 6.6 points on the ADHD-RS, ranging from 0 to 72 points, based on a trial by Zhang 2005, and a MIREDIF of 7.0 points on the CHQ, ranging from 0 to 100 points, based on a trial by Rentz 2005. We could find no references describing a MIREDIF on the CGI (range 0 to 30 points).

### *Unit of analysis issues*

Many ADHD trials use cross-over methods. We aimed to obtain data from the first period of these trials and to pool these

data with data from parallel-group trials, as they are similar (Curtin 2002). We requested these data from trial authors if they were not available in the published report. When we were not able to obtain first-period data from cross-over trials, we established another group comprising only endpoint data. Our original intention was to adjust for the effect of the unit of analysis error in cross-over trials by conducting a covariate analysis, but data were insufficient for this. As cross-over trials are more prone to bias from carry-over effects, period effects and unit of analysis errors (Curtin 2002), we conducted a subgroup analysis to compare these two groups. We tested for the possibility of a carry-over effect and a period effect ( Subgroup analysis and investigation of heterogeneity). We found similar treatment effects in the two groups and no significant subgroup differences. However, we noted considerable heterogeneity, and so we presented the results of the analyses separately (Effects of interventions).

For dichotomous outcomes in cross-over trials, we were unable to adjust the variance to account for the correlation coefficient as advised by Elbourne 2002 due to insufficient information, or to estimate the RR using the marginal probabilities as recommended by Becker 1993. Consequently, we used endpoint data for estimating RRs. As these effect estimates are prone to potential bias, we performed a sensitivity analysis by removing these trials to assess the robustness of the pooled results.

We used endpoint data when these were reported or could be obtained from trial authors. However, when RCTs reported only 'change scores', we pooled these with endpoint scores. We explored whether inclusion of change data affected outcomes by performing sensitivity analyses (see Sensitivity analysis).

### Dealing with missing data

We obtained missing data by contacting trial authors. When we were not able to obtain missing data, we conducted analyses using available (incomplete) data. Although some trials reported that intention-to-treat (ITT) analyses were used, data were missing for many primary outcomes (Hollis 1999). We could not use 'best-case scenario' and 'worst-case scenario' analyses on our assessment of benefit as there were no dichotomous outcomes. Also, we decided not to use 'best-case scenario' and 'worst-case scenario' analyses in our assessment of adverse events because we evaluated these analyses to be imprecise due to the high number of trials not reporting adverse events, and due to the high number of dropouts in the trials reporting adverse events.

### Assessment of heterogeneity

We identified three types of heterogeneity: clinical, methodological and statistical. Clinical heterogeneity reflects variability among participants, interventions and outcomes of trials. Methodological heterogeneity reflects variability in the design of trials, and statistical heterogeneity reflects differences in effect estimates between trials. We assessed clinical heterogeneity by comparing differences in trial populations, interventions and outcomes, and we evaluated methodological heterogeneity by comparing the design of trials. We identified potential reasons for clinical and methodological heterogeneity by examining individual trial characteristics and subgroups. Furthermore, we observed statistical heterogeneity in trials both by visual inspection of a forest plot and by use of a standard Chi² value with a significance level of α (alpha) = 0.1. We used $I^2$ to quantify inconsistency, with $I^2$ values between 30% and 60% indicating a moderate level of heterogeneity (Higgins 2011).

### Assessment of reporting biases

We followed the recommendations for reporting bias, including publication bias and outcome reporting bias, provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We drew funnel plots (estimated differences in treatment effects against their standard error) and performed Egger's statistical test for small-study effects; asymmetry could be due to publication bias or could indicate genuine heterogeneity between small and large trials (Higgins 2011). We did not visually inspect the funnel plot if fewer than 10 trials were included in the meta-analysis, in accordance with the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

### Data synthesis

We performed statistical analyses as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* ( Higgins 2011). We synthesised data statistically when clinical heterogeneity was not excessive (e.g. variability in participant characteristics was minimal). Furthermore, we included and analysed trials undertaken in any configuration or setting (e.g. in groups, at home, at a centre).

We used the inverse variance method, which gives greater weight to larger trials, to generate more precise estimates. For some adverse events we combined dichotomous data and continuous data using the generic inverse variance method. We synthesised data using change from baseline scores or endpoint data. If data were available for several intervals, we used the longest period assessed. We used both the fixed-effect and the random-effects models in all meta-analyses. However, we reported the results of the random-effects model, which gives greater weight to smaller trials; statistical significance did not change when we applied a fixed-effect model (Jakobsen 2014). We performed separate meta-analyses for three types of raters (teachers, independent assessors, parents), for data from parallel-group trials combined with data from the first period of cross-over trials and for endpoint data derived from cross-over trials.

ADHD symptom scales describe the severity of inattention, hyperactivity and impulsivity at home and at school; high scores indicate severe ADHD. We judged that, in spite of the diversity of psychometric instruments, they could be used for our outcomes, and we integrated different types of scales into the analyses. We used MDs if the same measure was used in all trials and SMDs when different outcome measures were used for the same construct in different trials.

When separate measures of hyperactivity, impulsivity and inattention were available, we used combined scores. When symptoms were measured and reported at different time points during the day (after ingestion of medication or placebo), we

used the time point closest to noon.

Two outcomes - ADHD symptoms and general behaviour - were measured by three types of raters: teachers, independent assessors and parents. We considered these data as showing different outcomes. We presented the results of teacher-rated measures as the primary outcome because symptoms of ADHD are more readily detectable in the school setting (Hartman 2007).

When trials reported data for different doses, we used data for the dose that we defined as moderate/high (> 20 mg/d) in our primary analyses.

We summarised adverse event data as RRs with 95% CIs for dichotomous outcomes. For the purposes of this review, we used only dichotomous outcomes that reflected the number of participants affected by the event per the total number of participants.

### *Heterogeneity-adjusted required information size and Trial Sequential Analysis*

Trial Sequential Analysis is a method that combines the required information size (RIS) for a meta-analysis with the threshold for statistical significance (Brok 2008; Brok 2009; Thorlund 2009; Wetterslev 2008) to quantify the statistical reliability of data in a cumulative meta-analysis, with P value thresholds controlled for sparse data and repetitive testing of accumulating data ( Brok 2008; Brok 2009; Thorlund 2009; Wetterslev 2008).

Comparable with the a priori sample size estimation provided in a single RCT, a meta-analysis should include an RIS at least as large as the sample size of an adequately powered single trial to reduce the risk of random error. A Trial Sequential Analysis calculates the RIS in a meta-analysis and provides trial sequential monitoring boundaries with an adjusted P value.

When new trials emerge, multiple analyses of accumulating data lead to repeated significant testing and hence introduce multiplicity. Use of conventional P values exacerbates the risk of random error (Berkey 1996; Lau 1995). Meta-analyses not reaching the RIS are analysed with trial sequential monitoring boundaries analogous to interim monitoring boundaries in a single trial (Wetterslev 2008). This approach will be crucial in coming updates of this review.

If a Trial Sequential Analysis does not result in significant findings (no Z-curve crossing the trial sequential monitoring boundaries) before the RIS has been reached, the conclusion should be that more trials are needed to reject or accept an intervention effect that was used to calculate the required sample size, or when the cumulated Z-curve enters the futility area, the anticipated intervention effect should be rejected.

For calculations with the Trial Sequential Analysis programme, we included trials with zero events by substituting 0.5 for zero (CTU 2011; Thorlund 2011).

For the outcomes 'total serious adverse events' and 'total non-serious adverse events', we calculated the a priori diversity-adjusted required information size (DARIS; i.e. number of participants in the meta-analysis required to detect or reject a specific intervention effect) and performed a Trial Sequential Analysis for these outcomes based on the following assumptions (Brok 2008; Brok 2009; Thorlund 2009; Wetterslev 2008; Wetterslev 2009).

1. Proportion of participants in the control group with adverse events.
2. Relative risk reduction of 20% (25% on 'total serious adverse events').
3. Type I error of 5%.
4. Type II error of 20%.
5. Observed diversity of the meta-analysis.

### *'Summary of findings' tables*

We used the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach to construct a 'Summary of findings' table in which to document all review outcomes (GRADEpro 2014). The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. Considerations are due to within-trial risk of bias; directness of the evidence; heterogeneity of the data; precision of effect estimates; and risk of publication bias (Andrews 2013a; Andrews 2013b; Balshem 2011; Brunetti 2013; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h; Guyatt 2013a; Guyatt 2013b; Guyatt 2013c; Mustafa 2013). When possible, that is when the MD or the RR was available, we used the results from the Trial Sequential Analysis as the rating for imprecision (Jakobsen 2014). We reported two primary outcomes (teacher-rated ADHD symptoms and serious adverse events) and three secondary outcomes (non-serious adverse events, teacher-rated general behaviour, and quality of life) in Summary of findings table 1.

### *Subgroup analysis and investigation of heterogeneity*

We performed the following subgroup analyses of teacher-rated ADHD symptoms (primary outcome) to test the robustness of this estimate.

1. Age of participants (trials with participants aged 2 to 6 years versus those with participants aged 7 to 11 years versus those with participants aged 12 to 18 years).
2. Sex (boys versus girls).
3. Comorbidity (children with comorbid disorders versus children without comorbid disorders).
4. Type of ADHD (participants with predominantly inattentive subtype versus participants with predominantly combined subtype).

After learning about other factors that may affect the impact of methylphenidate, we performed the following additional post hoc subgroup analyses on teacher-rated ADHD symptoms to test the robustness of the estimate.

1. Types of scales (e.g. Conners' Teacher Rating Scale (CTRS; Conners 1998a) versus Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) Scale (Swanson 2006).
2. Dose of methylphenidate (low dose (≤ 20 mg/d or ≤ 0.6 mg/kg/d) versus moderate/high dose (> 20 mg/d or > 0.6 mg/kg/d)).
3. Duration of treatment (short-term trials (≤ six months) versus long-term trials (> six months)).
4. Trial design (parallel-group trials versus cross-over trials (first period data and endpoint data)).
5. Medication status before randomisation (medication naive (> 80% of included participants were medication naive) versus not medication naive (< 20% of included participants were medication naive)).
6. Risk of bias (trials with low risk of bias versus trials with high risk of bias).
7. Cohort selection bias (trials with cohort selection bias of all participants versus trials without cohort selection bias).

### *Sensitivity analysis*

We conducted sensitivity analyses to determine whether findings were sensitive to the following.

1. Decisions made during the review process such as our assessment of clinical heterogeneity (listed below).
2. Combined 'change scores' and 'endpoint data' in the meta-analyses.

No sufficiently well-designed method has been used to combine the results of trials with high risk of bias and trials with low risk of bias (Higgins 2011). We performed sensitivity analyses by grouping together trials with similar classifications of bias, as described above, and investigated the impact on intervention effects.

We excluded the following trials from the sensitivity analyses.

1. IQ < 70: Oesterheld 1998; Pearson 2013; Smith 1998; Taylor 1987.
2. Change scores: Carlson 2007; Findling 2007; Newcorn 2008; Palumbo 2008; Tucker 2009.
3. Older than 18 years of age: Green 2011; Szobot 2008.

# Results

## Description of studies

For more information, please see Characteristics of included studies, Characteristics of excluded studies, Characteristics of studies awaiting classification and Characteristics of ongoing studies.

### *Results of the search*

We carried out electronic searches over four periods. Searches up to October 2011 produced 6358 records after duplicates were removed (10,249 initial records). Searches up to November 2012 produced an additional 713 records after duplicates were removed (1080 initial records). Searches up to March 2014 produced an additional 654 records after duplicates were removed (1274 initial records). Searches up to February 2015 (ClinicalTrials.gov and ICTRP) and March 2015 (all remaining databases) produced an additional 1178 records after duplicates were removed (1460 initial records). We identified 368 additional publications by reading the reference lists of included articles and reviews, and by corresponding with authors of relevant literature and with pharmaceutical companies. We contacted the authors of 161 trials twice for supplemental information and data; 92 responded.

From the 9271 screened records, we excluded 7811 clearly irrelevant reports on the basis of title and abstract. We retrieved the full texts of the remaining 1460 reports, which we assessed for eligibility. Of the retrieved publications, 69 were written in languages other than English, including Danish, Norwegian, German, Dutch, French, Italian, Spanish, Portuguese, Czech, Turkish, Farsi, Japanese and Chinese; we had these articles translated to assess their eligibility. We excluded 691 full-text reports (please see subsection on Excluded studies and Characteristics of excluded studies tables), and identified 2 trials (from 2 reports) as awaiting classification (see Characteristics of studies awaiting classification), and 5 ongoing trials (from 6 reports; see Characteristics of ongoing studies). We included 761 reports, of which 449 described 185 RCTs and 312 described 243 non-randomised studies. (We are currently assessing and synthesising data from the 243 non-randomised studies. These findings will be published in the forthcoming review on adverse events in observational studies (Storebø in press). This review focuses on RCTs only (see Figure 1; Moher 2009). For more information on these trials, please see the Characteristics of included studies tables.

### *Included studies*

We included 185 trials (from 449 reports) in this review (Figure 1). Of these, 38 are parallel-group trials (from 138 reports) and 147 are cross-over trials (from 311 reports). One study - Kollins 2006 (PATS) - includes a parallel-group trial and a cross-over trial.

#### Included parallel-group trials

We included 38 parallel-group trials described in 138 reports.

**Duration**

Most trials (n = 34) were short-term (< six months in duration). Only three were long-term trials (conducted for ≥ six months; Jensen 1999 (MTA); Perez-Alvarez 2009; Schachar 1997a). The duration of one trial was unclear (Tucker 2009). Average trial duration was 74.8 days (range 1 to 425 days).

**Location**

Twenty-one of the 38 trials were conducted in the USA. Two trials were conducted in the USA and Canada (Biederman 2003;

Jensen 1999 (MTA)); one in the USA, Canada and Australia (Findling 2006); and one in USA, Canada, Taiwan, Mexico and Puerto Rico (Lin 2014). Two trials each were conducted in Brazil (Martins 2004; Szobot 2004), Canada (Butter 1983; Schachar 1997a), Israel (Green 2011; Jacobi-Polishook 2009) and Germany (Coghill 2013; Lehmkuhl 2002), although Coghill 2013 also included participants in Sweden. Single trials were conducted in New Zealand (Heriot 2008), Norway (Duric 2012) and the Netherlands (Van der Meere 1999a). The locations of two trials were not clear (Firestone 1981; Tourette's Syndrome Study Group 2002).

### Setting

All but the following three trials were conducted in out-patient clinics: one was carried out in a naturalistic classroom setting ( Greenhill 2006), one in a research unit at a hospital (Schachar 1997a), and one provided no information on setting (Brown 1985).

### Participants

The 38 trials included a total of 5111 participants (with the percentage of girls ranging from 0% to 50% (mean 20.7%), equivalent to a boy-to-girl ratio of 5:1). All participants were between 3 and 20 years of age (mean 9.7 years).

Twenty-six trials described the percentage of methylphenidate-naive participants (range 0% to 100%; mean 58.2%).

Twenty-three trials described the proportion of participants with combined subtype ADHD (range 25% to 100%; mean 72%); 19 trials reported the proportion of participants with hyperactive subtype (range 0% to 56%; mean 5%) and 20 trials revealed the proportion with inattentive subtype (range 0% to 72.4%; mean 24%).

Five trials excluded children and adolescents with a comorbidity (Findling 2010; Greenhill 2002; Perez-Alvarez 2009; Tucker 2009; Wigal 2004), but it was not clear whether such participants were included in 11 trials (Arnold 2004; Biederman 2003; Brown 1985; Butter 1983; Duric 2012; Findling 2006; Findling 2008; Firestone 1981; Greenhill 2006; Jacobi-Polishook 2009; Wilens 2006b). Oppositional defiant disorder was the most common comorbidity (range 8% to 53%; mean 36.3%), followed by conduct disorder (range 2% to 32%; mean 11.6%).

Participants taking other medications were specifically excluded from 10 trials (Green 2011; Heriot 2008; Ialongo 1994; Jacobi-Polishook 2009; Kollins 2006 (PATS); Martins 2004; Palumbo 2008; Perez-Alvarez 2009; Schachar 1997a; Wigal 2004), and were permitted in two trials (Lehmkuhl 2002; Van der Meere 1999a). Riggs 2011 allowed inclusion of participants using drugs and alcohol.

### Interventions

Twelve trials used extended- and modified-release methylphenidate (Biederman 2003; Childress 2009; Coghill 2013; Green 2011; Greenhill 2002; Greenhill 2006; Lehmkuhl 2002; Lin 2014; Newcorn 2008; Riggs 2011; Tucker 2009; Wilens 2006b). Two trials used immediate- and extended-release methylphenidate (Findling 2006; Wolraich 2001), and two trials used transdermal methylphenidate patches (Findling 2008; Findling 2010). All other trials used immediate-release methylphenidate.

The method of reporting the dosage of methylphenidate varied considerably between trials, but overall daily dose ranged from 5 mg to 60 mg with a mean reported total daily dose of 28.2 mg/d or 0.73 mg/kg/d. The average dose of any type of modified- or extended-release methylphenidate was 41.0 mg, and the average dose of immediate-release methylphenidate was 23.1 mg.

Twenty-eight trials used placebo as control, and 10 trials used no intervention as control (Brown 1985; Connor 2000; Duric 2012; Firestone 1981; Heriot 2008; Jensen 1999 (MTA); Perez-Alvarez 2009; Riggs 2011; Schachar 1997a; Tucker 2009).

Four trials used clonidine (Connor 2000; Palumbo 2008; Tourette's Syndrome Study Group 2002) or atomoxetine (Carlson 2007) as a cointervention in both intervention and control groups. Three trials used parent training (Firestone 1981; Heriot 2008; Schachar 1997a), two used cognitive-behavioural therapy (Brown 1985; Riggs 2011) and five used other behavioural therapies (Duric 2012; Horn 1991; Jensen 1999 (MTA); Perez-Alvarez 2009; Tucker 2009) as cointerventions for intervention and control groups.

## Included cross-over trials

We included 147 cross-over trials described in 311 reports.

Eighty-three trials were described in a single publication. Ten trials yielded five or more publications (Brams 2012; Döpfner 2004; Gadow 1995; Grizenko 2012; Kollins 2006 (PATS); Rapport 1987; Sharp 1999; Swanson 2002a; Swanson 2002b; Swanson 2004b). The PATS (Preschool Attention Deficit Hyperactivity Disorder Treatment Study) trial reported the greatest number of publications per trial, with 23 publications (Kollins 2006 (PATS).

### Duration

Three cross-over trials did not report duration (Kelly 1989; Sunohara 1999; Tannock 1993). The remaining cross-over trials had a duration of less than six months.

### Location

A total of 103 trials were carried out in the USA; 21 in Canada; and one in both the USA and Canada (Quinn 2004). Five trials were conducted in Israel (Lufi 1997; Lufi 2007; Moshe 2012; Tirosh 1993a; Tirosh 1993b); five in Germany (Bliznakova 2007; Döpfner 2004; Konrad 2004; Konrad 2005; Schulz 2010); four in the Netherlands (Buitelaar 1995; Flapper 2008; Lijffijt 2006; Overtoom 2003); two each in the UK (Coghill 2007; Taylor 1987), Norway (Ramtvedt 2013; Zeiner 1999) and Brazil ( Szobot 2008; Zeni 2009); and one in Australia (Nikles 2006). One trial did not specify the country of origin (Hicks 1985).

### Setting

Seventeen trials were completed as a part of summer treatment programmes or summer schools. Five trials were conducted in in-patient wards (Carlson 1995; Gonzalez-Heydrich 2010; Kent 1995; Konrad 2005; Solanto 2009), and five in both out-patient clinics and in-patient wards (Garfinkel 1983; Hicks 1985; Kaplan 1990; Konrad 2004; Wallander 1987). Twelve trials were conducted in a laboratory classroom setting (Brams 2008; Lopez 2003; Oesterheld 1998; Schachar 2008; Sharp 1999; Silva 2006; Swanson 1998; Swanson 1999; Swanson 2002a; Swanson 2002b; Wigal 2003; Wigal 2014). Eight trials did not report the setting (Ben 2002; Bliznakova 2007; Froehlich 2011; Pliszka 2007; Stoner 1994; Tervo 2002; Ullmann 1985; Urman 1995). All remaining trials were conducted in out-patient clinics only.

### Participants

The 147 cross-over trials included a total of 7134 participants (range 1 to 430 per trial; mean 48.5). In 131 of these trials, a total of 6597 participants were randomly assigned, 6018 of whom were followed up in analyses. In 13 trials, 537 participants were randomly assigned, but it was unclear how many participants were followed up (Ben 2002; Chronis 2003; Coghill 2007; Douglas 1995; Fitzpatrick 1992a; Gadow 2011; Hale 2011; Leddy 2009; Pelham 1989; Rapport 1987; Shiels 2009; Smithee 1998; Wallander 1987). In two trials, it was unclear how many participants were included, but 191 were followed up in analyses (Epstein 2011; Sharp 1999). In one trial, it was unclear how many participants were included or followed up ( Rapport 1987).

Nine trials did not state the ratio of boys to girls (Epstein 2011; Fine 1993; Leddy 2009; Pliszka 1990; Rapport 1987; Samuels 2006; Solanto 2009; Sumner 2010; Wallace 1994), and 30 trials did not specifically comprise girls. In the 108 trials that included participants of both sexes and reported proportions, the percentage of girls ranged from 4% to 50% (mean 21.8%). Participants were between 4 and 21 years of age with an average age of 9.7 years (17 trials did not report average age; however, all of these trials reported age range).

A total of 98 trials described the percentage of methylphenidate-naive participants included (range 0% to 100%; mean 51%). In 26 trials, all participants were methylphenidate naive. Only participants previously treated with methylphenidate were included in 30 trials.

Sixty-four trials described the proportion of participants with combined subtype ADHD (range 0% to 100%; mean 69.1%), 63 reported the proportion with hyperactive subtype (range 0% to 100%; mean 12.3%) and 63 reported the proportion with inattentive subtype (range 0% to 72%; mean 20.2%).

Eighty-eight trials reported the presence of comorbidity. Oppositional defiant disorder was the most commonly reported comorbidity (61 trials; range 1.4% to 84%; mean 42%), followed by conduct disorder (49 trials; range 0% to 100%; mean 24%). Four trials reported participants with Tourette's syndrome (range 12% to 100%; mean 75%; Castellanos 1997; Gadow 2007; Gadow 2011; Kent 1999). One trial included only participants with epilepsy (Gonzalez-Heydrich 2010), one included only participants with cerebral palsy (Symons 2007), and one included only participants with bipolar disorder (Findling 2007). Fourteen trials reported that participants had no comorbidity (Borcherding 1990; Brams 2012; Garfinkel 1983; Lufi 1997; Moshe 2012; Quinn 2004; Schachar 2008; Sumner 2010; Swanson 1998; Swanson 2002a; Tirosh 1993a; Tirosh 1993b; Wilens 2008; Wilkison 1995).

Thirteen trials reported that participants were taking other medications (Buitelaar 1995; Carlson 1995; Castellanos 1997; Cox 2006; Findling 2007; Gadow 2007; Gonzalez-Heydrich 2010; Kaplan 1990; McBride 1988a; Pearson 2013; Pelham 1989; Szobot 2008; Zeni 2009), and 42 trials stated that comedication was not used. It was not clear whether the remaining 92 trials permitted comedication.

### Interventions

In all, 101 trials reported use of a single type of methylphenidate (without specifying the type), whereas 12 trials reported use of a single type of immediate-release methylphenidate (Ahmann 1993; Chronis 2003; Fabiano 2007; Gadow 2007; Johnston 1988; Kollins 2006 (PATS); Moshe 2012; Smith 2004; Solanto 2009; Swanson 1999; Swanson 2002a; Tervo 2002), and 19 reported use of a single type of extended-release methylphenidate. Seven trials used both immediate- and extended-release methylphenidate (Döpfner 2004; Fitzpatrick 1992a; Pelham 1990a; Pelham 2001a; Schachar 2008; Swanson 2002b; Wigal 2003), four trials used two different types of extended-release methylphenidate (Lopez 2003; Schulz 2010; Silva 2005a; Swanson 2004b), and four used transdermal methylphenidate patches (Pelham 2005; Pelham 2011; Wilens 2008; Wilens 2010).

The method of reporting the dose of methylphenidate varied considerably between trials, and three trials did not report dose ( Bliznakova 2007; Nikles 2006; Wallace 1994). Overall daily dose ranged from 4 mg to 77 mg, with mean reported total daily dose of 24.5 mg or 0.6 mg/kg. Doses of immediate-release methylphenidate ranged from 4 mg to 54 mg, with mean reported total daily dose of 25 mg or 0.7 mg/kg. Doses of extended-release methylphenidate ranged from 15 mg to 77 mg, with mean reported total daily dose of 36 mg or 1.1 mg/kg. Duration of methylphenidate treatment ranged from 1 to 56 days, with an average duration of 15.6 days.

All trials used placebos as control.

Three trials used concomitant cointerventions (antidepressant: Carlson 1995; behaviour modification: Kolko 1999; and antipsychotic: Zeni 2009) in both intervention and control groups.

## Outcomes

Some psychometric ADHD instruments measured total score for ADHD symptoms, whereas others assessed only specific symptom domains of ADHD (e.g. inattention, hyperactivity, impulsivity). We categorised all scales into five subgroups: ADHD

symptoms; serious adverse events; non-serious adverse events; general behaviour; and quality of life. Some psychometric instruments are abbreviated versions or revised versions, but all have been validated.

#### ADHD symptoms

Conners' questionnaires were the most frequently used measures of ADHD symptoms; more than 30 different versions measured core symptoms of ADHD (normative data are generally well intercorrelated in revised versions; Goyette 1978).

Table 1 presents the list of all measures used to assess ADHD symptoms in the included trials. This list primarily refers to original articles describing the psychometric properties of measurement scales, but in a few cases, we refer to trials describing use of a specific measurement scale.

#### Serious and non-serious adverse events

Adverse events were measured by rating scales or by spontaneous reports and/or were recorded by investigators at regular interviews or visits. Some trials included physical examinations or paraclinical examinations, or both, such as blood testing, electrocardiogram (ECG), blood pressure reading, measurement of heart rate and assessment of weight and height. Serious adverse events were recorded in accordance with the ICH classification (ICH 1996). However, when in doubt, we asked trial authors which classification or definition they had used in their trial.

Some trials combined all of the above modes of measurement; others used a single measure such as spontaneous reports or rating scales. Fifty-two trials employed rating scales; the Barkley Side Effects Rating Scale (SERS) was used most frequently (Barkley 1990).

Other scales used included the Significant Adverse Event Reviews Questionnaire (SAERS; Barkley 1990; Zeni 2009), the Pittsburgh Side Effect Rating Scale (PSERS; Pelham 1993b; Pelham 2005a) and Subject's Treatment Emergent Symptom Scale (STESS; Guy 1976a).

For the purpose of measuring specific adverse events, some trials used rating scales such as Paediatric Sleep Questionnaire (PSQ; Chervin 2000), Sleep Disturbances Scale for Children (SDSC; Bruni 1996), Children's Sleep Habits Questionnaire (CSHQ; Owens 2000), Child Depression Rating Scale (CDRS-R; Poznanski 1983), Young Mania Rating Scale (YMRS; Young 1978), Yale Global Tic Severity Scale (YGTSS; Leckman 1989), Tic Symptom Self Report Scale (TSSR; Leckman 1988), and the Massachusetts General Hospital (MGH) Abuse and Diversion Questionnaire (Wilens 2006a).

#### General behaviour

Many different scales can be used to assess general behaviour. These scales have different foci, such as aggression or oppositional behaviour, but all describe participants' behaviour and the influence of methylphenidate. Higher scores on general behaviour symptom scales signify better outcomes.

Table 2 presents the list of all measures used to assess general behaviour. This list refers primarily to the original articles describing the psychometric properties of measurement scales used to measure general behaviour in the included trials. In a few cases, we refer to trials that describe use of a specific measurement scale.

#### Quality of life

Seven scales measured quality of life in relation to both ADHD and life in general. All of these scales produced higher values equating to better health. Only three could be used in meta-analyses: Child Health Questionnaire (CHQ; Landgraf 1998); Children's Global Assessment Scale (CGAS; Shaffer 1983); and Child Health and Illness Profile, Child Edition: Parent Report Form (CHIP-CE:PRF; Riley 2004).

See Table 3 for additional information on types of rating scales used to assess quality of life in the included trials.

### *Excluded studies*

We have taken a very inclusive approach by reading 1460 full text reports, 603 of which were subsequently excluded for the following reasons: 367 reports of non-randomised studies, 131 reports with no description of an acceptable ADHD diagnosis, 15 reports describing no treatment with methylphenidate, 5 reports that only included patients older than 18 years of age, 40 reports of patients with a IQ below 70, 31 reports with polypharmacy, and 14 reports excluded for various 'other' reasons (see Figure 1).

We formally excluded 78 trials (88 reports) that examined the impact of methylphenidate on very specific domains that were outside the focus of this review such as motor co-ordination, reaction time, memory tasks, and reading skills. For more information on these trials, please see Characteristics of excluded studies tables.

## Risk of bias in included studies

We assessed the risk of bias of each included trial using the Cochrane 'Risk of bias' tool (Higgins 2011). A summary of our assessment is displayed in Figure 2 and Figure 3. As shown, we assessed six cross-over trials (3%) as having low risk of bias in all domains. We assessed the remaining 179 trials (97%) as trials with high risk of bias. However, even the six cross-over trials had likely breaks in their blinding due to prevalent adverse events to methylphenidate (see below). Accordingly, we judged all 185 trials to be trials with high risk of bias.

### *Parallel-group trials*

None of the 38 included parallel-group trials had low risk of bias in all bias domains.

### *Allocation (selection bias)*

Random sequence generation

We considered random sequence generation to be at low risk of bias in 22 trials, at high risk of bias in 3 trials (Connor 2000; Green 2011; Heriot 2008), and at unclear risk of bias in 13 trials (Brown 1985; Butter 1983; Findling 2006; Firestone 1981; Greenhill 2002; Greenhill 2006; Ialongo 1994; Lin 2014 ; Newcorn 2008; Perez-Alvarez 2009; Tucker 2009; Wigal 2004; Wilens 2006).

#### Allocation concealment

We considered allocation concealment to be at low risk of bias in 18 trials, at high risk of bias in 1 trial (Green 2011; Szobot 2008), and insufficiently reported in 19 trials.

### *Blinding (performance bias and detection bias)*

We considered the method of blinding of participants and personnel to be adequately described in 28 trials but insufficiently reported in 6 trials (Biederman 2003; Childress 2009; Findling 2010; Greenhill 2006; Lin 2014; Tucker 2009). Four trials were not blinded (Brown 1985; Duric 2012; Jensen 1999 (MTA); Perez-Alvarez 2009).

We considered the method of blinding of outcome assessment to be adequately described in 23 trials but insufficiently reported in 11 trials (Biederman 2003; Butter 1983; Childress 2009; Findling 2006; Findling 2008; Findling 2010; Green 2011; Greenhill 2002; Greenhill 2006; Lin 2014; Martins 2004). Four trials did not include blinded outcome assessors (Brown 1985; Duric 2012; Jensen 1999 (MTA); Perez-Alvarez 2009).

### *Incomplete outcome data (attrition bias)*

Twenty-four trials adequately addressed incomplete data, and 10 trials did not (Findling 2006; Findling 2008; Findling 2010; Heriot 2008; Ialongo 1994; Lin 2014; Pliszka 2000; Schachar 1997; Tucker 2009; Wilens 2006). In four trials information was insufficient for assessment of whether the method used to handle missing data was likely to bias the estimate of effect ( Coghill 2013; Firestone 1981; Palumbo 2008; Wigal 2004).

### *Selective reporting (reporting bias)*

Twenty-five trials reported all pre-defined or otherwise expected outcomes, and two trials did not (Greenhill 2006; Lin 2014). In 11 trials it was unclear whether trial authors reported all pre-defined or otherwise expected outcomes (Butter 1983; Firestone 1981; Greenhill 2002; Heriot 2008; Horn 1991; Ialongo 1994; Perez-Alvarez 2009; Schachar 1997; Szobot 2004; Tucker 2009; Wolraich 2001).

### *Vested interests (industry bias)*

Twenty-two trials were funded by industry. In seven trials information was insufficient for assessment of whether potential vested interests were likely to bias the estimate of effect (Horn 1991; Ialongo 1994; Jacobi-Polishook 2009; Martins 2004; Schachar 1997a; Tourette's Syndrome Study Group 2002; Riggs 2011). No vested interests were described in the remaining nine trials (Brown 1985; Butter 1983; Connor 2000; Duric 2012; Firestone 1981; Green 2011; Heriot 2008; Jensen 1999 (MTA); Perez-Alvarez 2009).

### *Other potential sources of bias*

We identified no other sources of bias.

### *Cross-over trials*

Only 6 of the 147 included cross-over trials had low risk of bias in all bias domains (DuPaul 1996; Flapper 2008; Gorman 2006; Rapport 2008; Stein 1996; Wilkison 1995), and even these were considered at risk of deblinding due to prevalent adverse events (see below).

### *Allocation (selection bias)*

#### Random sequence generation

We considered random sequence generation to be at low risk of bias in 58 trials, at high risk of bias in 10 trials (Carlson 1995 ; Fitzpatrick 1992a; Kaplan 1990; Kelly 1989; Manos 1999; McBride 1988a; Szobot 2008; Tirosh 1993b; Whalen 1990; Wigal 2014), and at unclear risk of bias in 79 trials.

#### Allocation concealment

We considered allocation concealment to be at low risk of bias in 53 trials, at high risk of bias in 5 trials (Carlson 1995; Fitzpatrick 1992a; Szobot 2008; Ullmann 1985; Wigal 2014), and not sufficiently reported in 89 trials.

### *Blinding (performance bias and detection bias)*

We judged the method of blinding of participants and personnel to be adequately described in 109 trials but unclear in 29 trials. Nine trials were not blinded (Lopez 2003; Manos 1999; Pearson 2013; Pelham 2014; Ramtvedt 2013; Stein 2003; Ullmann 1985; Whalen 1990; Wigal 2013).

We judged the method of blinding of outcome assessment to be adequately described in 79 trials but unclear in 62 trials. Six trials did not include blinded outcome assessors (Cox 2006; Douglas 1986; Manos 1999; Whalen 1990; Wigal 2013; Wodrich 1998).

### *Incomplete outcome data (attrition bias)*

Sixty-four trials adequately addressed incomplete data. In 54 trials information was insufficient for assessment of whether the method used to handle missing data was likely to bias the estimate of effect. Twenty-nine trials had incomplete outcome

data.

### *Selective reporting (reporting bias)*

Forty-nine trials reported all pre-defined or otherwise expected outcomes, and eight trials did not (Castellanos 1997; Chacko 2005; Gonzalez-Heydrich 2010; McGough 2006; McInnes 2007; Stein 2003; Sunohara 1999; Taylor 1993). In 90 trials it was unclear whether trial authors reported all pre-defined or otherwise expected outcomes.

### *Vested interests (industry bias)*

Fifty trials were funded by industry. In 41 trials we judged information to be insufficient for assessment of whether potential vested interests were likely to bias the estimate of effect. The remaining 56 trials reported no vested interests.

### *Other potential sources of bias*

We identified no other sources of bias.

### *Cohort selection bias of all participants*

Ten parallel-group trials and 49 cross-over trials excluded methylphenidate non-responders, placebo responders and/or patients with methylphenidate adverse events before randomisation. Such trials have limited external validity.

## Effects of interventions

Below, we present the results of meta-analyses performed for two primary outcomes (ADHD symptoms and serious adverse events) and three secondary outcomes (non-serious adverse events, general behaviour and quality of life). For a summary of key results, please see Summary of findings table 1.

### *Comparison: methylphenidate versus placebo or no intervention*

Primary outcomes

**ADHD symptoms**

We were able to combine data on ADHD symptoms from 25 parallel-group trials and 74 cross-over trials. The evidence was assessed to be of very low quality (see GRADE assessment below).

*Teacher-rated ADHD symptoms*

Parallel-group trials and cross-over trials (first period data only)

Meta-analysis suggested that methylphenidate significantly reduced teacher-rated ADHD symptoms compared with placebo (standardised mean difference (SMD) -0.77, 95% confidence interval (CI) -0.90 to -0.64; $I^2$ = 37%; 19 trials, 1698 participants; Analysis 1.1). The SMD of -0.77 for ADHD symptoms corresponds to a mean difference (MD) of -9.6 points (95% CI -13.7 to -6.4) on the ADHD Rating Scale (DuPaul 1991a).

Our subgroup analyses revealed that the intervention effect varied according to the following.

1. Types of scales used (test for subgroup differences: $Chi^2$ = 24.81, df = 10 (P value = 0.006); $I^2$ = 59.7%; Analysis 1.2).
2. Medication status before randomisation, with a seemingly better effect in trials with no medication-naive patients (SMD -1.06, 95% CI -1.33 to -0.79; $I^2$ = 0%; 2 trials, 286 participants) compared to trials with medication-naive patients (SMD -0.63, 95% CI -0.94 to -0.31; $I^2$ = 51%; 4 trials, 431 participants (test for subgroup differences: $Chi^2$ = 4.18, df = 1 (P value = 0.04); $I^2$ = 76.1%; Analysis 1.3).
3. Duration of treatment, with seemingly lesser effect in long-term trials (SMD -0.47, 95% CI -0.72 to -0.22; 1 trial, 253 participants) compared to short-term trials (SMD -0.81, 95% CI -0.94 to -0.68; $I^2$ = 25%; 18 trials, 1445 participants) (test for subgroup difference: $Chi^2$ = 5.37, df = 1 (P value = 0.02); $I^2$ = 81.4%; Analysis 1.4). The SMD effect of -0.47 for ADHD long-term trials corresponds to an MD of only -5.75 points (95% CI -4.2 to -9.2) on the ADHD-RS (DuPaul 1991a).

No evidence suggested that dose (Analysis 1.5), trial design (Analysis 1.6) or risk of cohort selection bias (Analysis 1.7) influenced the estimated intervention effect. All 19 trials were at high risk of bias (Analysis 1.1). Inspection of the funnel plot in Figure 4 suggested potential bias (asymmetry), although we found no evidence of significant publication bias: Egger's regression intercept (bias) was -0.2260 (two-tailed, P value = 0.81). Finally, one of the trials in this meta-analysis used change from baselines scores (Palumbo 2008), but removing this trial did not significantly change the estimate.

Cross-over trials (endpoint data)

Meta-analysis suggested that methylphenidate significantly reduced teacher-rated ADHD symptoms compared with placebo (SMD -0.93, 95% CI -1.06 to -0.80; $I^2$ = 77%; 59 trials, 5145 participants; Analysis 1.8). The estimated intervention effect did not vary according to risk of bias (Analysis 1.8), but did vary according to dose of methylphenidate (Analysis 1.9). Three of these trials included some participants with an IQ less than 70 (Pearson 2013; Smith 1998; Taylor 1987). Removing these trials did not significantly change the estimate.

Parallel-group trials and cross-over trials (endpoint data)

Meta-analysis suggested that methylphenidate significantly reduced teacher-rated ADHD symptoms compared with placebo (SMD -0.91, 95% CI -1.01 to -0.80; $I^2$ = 72%; 75 trials, 6344 participants; Analysis 1.10). No evidence suggested that the intervention effect varied according to risk of bias (low risk of bias versus high risk of bias; Analysis 1.11).

*Independent assessor-rated ADHD symptoms*

Most independent assessors were clinicians.

Parallel-group trials and cross-over trials (first period data only)

Meta-analysis suggested that methylphenidate significantly reduced independent assessor-rated ADHD symptoms compared with placebo (SMD -0.64, 95% CI -0.89 to -0.39; I² = 85%; 10 trials, 1907 participants; Analysis 2.1). The SMD effect of -0.64 for ADHD symptoms corresponds to an MD of -8.0 points (95% CI -5.8 to -12.5) on the ADHD-RS (DuPaul 1991a). No evidence indicated that the intervention effect was influenced by types of scales (Analysis 2.2), duration of treatment ( Analysis 2.3), trial design (Analysis 2.4) or risk of cohort selection bias (Analysis 2.5). We were unable to test for subgroup differences according to dose, as no low-dose methylphenidate trials were identified (Analysis 2.6). All 10 trials were at high risk of bias (Analysis 2.1). Two trials reported change from baseline scores (Findling 2008; Newcorn 2008). Removing these trials did not significantly change the estimate.

Cross-over trials (endpoint data)

Meta-analysis suggested that methylphenidate significantly reduced independent assessor-rated ADHD symptoms compared with placebo (SMD -1.00, 95% CI -1.16 to -0.84; I² = 69%; 19 trials, 2471 participants; Analysis 2.7). All 19 trials were at high risk of bias (Analysis 2.7). The intervention effect was significantly influenced by the dose of methylphenidate, with the highest estimate reported in the high-dose group (SMD -1.13, 95% CI -1.31 to -0.95; I² = 66%; 12 trials, 1853 participants; Analysis 2.8).

Parallel-group trials and cross-over trials (endpoint data)

Meta-analysis suggested that methylphenidate significantly reduced independent assessor-rated ADHD symptoms compared with placebo (SMD -0.83, 95% CI -0.98 to -0.67; I² = 82%; 28 trials, 4215 participants; Analysis 2.9).

*Parent-rated ADHD symptoms*

Parallel-group trials and cross-over trials (first period data only)

Meta-analysis suggested that methylphenidate significantly reduced parent-rated ADHD symptoms compared with placebo (SMD -0.66, 95% CI -0.82 to -0.51; I² = 60%; 21 trials, 2187 participants; Analysis 3.1). The SMD effect of -0.66 for ADHD symptoms corresponds to an MD of -8.2 points (95% CI -6.0 to 12.9) on the ADHD-RS (DuPaul 1991a). We found evidence that the intervention effect varied by types of scales (test for subgroup differences: Chi² = 22.34, df = 10 (P value = 0.01); I² = 55.2%; Analysis 3.2). However, duration of treatment (Analysis 3.3), dose of methylphenidate (Analysis 3.4), medication status before randomisation (Analysis 3.5), risk of cohort selection bias (Analysis 3.6) and trial design (Analysis 3.7) did not seem to significantly influence the intervention effect. All 21 trials were at high risk of bias (Analysis 3.1). Two trials in the meta-analysis reported change from baseline scores (Carlson 2007; Tucker 2009), but removing these trials did not significantly change the estimate.

Cross-over trials (endpoint data)

Meta-analysis suggested that methylphenidate significantly reduced parent-rated ADHD symptoms compared with placebo (SMD -0.78 (95% CI -0.90 to -0.67; I² = 59%; 41 trials, 3734 participants; Analysis 3.8). This effect was not significantly influenced by risk of bias (Analysis 3.8) or dose of methylphenidate (Analysis 3.9). Two trials included some participants with an IQ less than 70 (Pearson 2013; Taylor 1987), but removing these trials did not significantly change the estimate.

Parallel-group trials and cross-over trials (endpoint data)

We observed comparable findings when combining data from parallel-group trials with endpoint data from cross-over trials (SMD -0.74, 95% CI -0.83 to -0.65; I² = 58%; 59 trials, 5861 participants; Analysis 3.10).

*Additional subgroup analyses*

We tested for differences between raters (teachers, independent assessors and parents) and found no significant differences (test for subgroup differences: Chi² = 2.00, df = 2 (P value = 0.37); I² = 0.0%; Analysis 4.1).

We found no evidence suggesting that age (Analysis 4.2) or comorbidity influenced the intervention effect (Analysis 4.3). However, the intervention effect was significantly influenced by ADHD subtype, with a greater intervention effect noted for the inattentive subtype (SMD -1.31, 95% CI -1.61 to -1.01; 1 trial, 204 participants) compared with the combined subtype (SMD 0.65, 95% CI -1.30 to 2.60; I² = 99%; 2 trials, 559 participants) (test for subgroup differences: Chi² = 3.79, df = 1 (P value = 0.05); I² = 73.6%; Analysis 4.4). This difference rested upon one single trial.

We found no evidence of a 'carry-over effect' in the cross-over trials. We conducted a subgroup analysis to investigate the difference between first period data and endpoint data from four cross-over trials (372 participants), and we found no significant subgroup differences (test for subgroup differences: Chi² = 2.47, df = 1 (P value = 0.12); I² = 59.6%; Analysis 4.5).

**Numbers of serious adverse events**

We were able to combine data on serious adverse events from nine parallel-group trials (Carlson 2007; Childress 2009; Coghill 2013; Findling 2010; Jacobi-Polishook 2009; Lehmkuhl 2002; Palumbo 2008; Riggs 2011; Wolraich 2001) and eight cross-over trials (Brams 2008; Brams 2012; Buitelaar 1995; Cox 2006; Grizenko 2012; Schachar 2008; Silva 2008; Wigal 2013).

The evidence was assessed to be of very low quality (see GRADE assessment below). Therefore, we cannot exclude that harms may be worse than reported.

*Parallel-group trials and cross-over trials (first period data only)*

We found no significant differences between participants in the methylphenidate group and those in the control group as regards the numbers of serious adverse events (RR 0.98, 95% CI 0.44 to 2.22; 9 trials, 1532 participants; Analysis 5.1), and

we found no evidence of heterogeneity between trials ($I^2$ = 0%).

Serious adverse events reported by participants in the methylphenidate group were cyst rupture (n = 1), kidney infection (n = 1) and psychosis (n = 2). Serious adverse events reported by participants in the control group included loss of consciousness (n = 1), drug toxicity (n = 1), asthma (n = 1) and concussion (n = 1). Severe adverse events reported by both groups included syncope (methylphenidate n = 3, control n = 1) and aggression (methylphenidate n = 1, control n = 2) (Analysis 5.1).

*Cross-over trials (endpoint data)*

We found no differences between those in the methylphenidate group and individuals in the control group regarding the incidence of serious adverse events (RR 1.62, 95% CI 0.34 to 7.71; $I^2$ = 0%; 8 trials; n = 1721; Analysis 6.1). However, data from only four trials contributed to this meta-analysis because zero events were reported in the other four trials.

*Trial Sequential Analysis*

We conducted a Trial Sequential Analysis on the 'total serious adverse events' outcome, involving nine parallel-group trials. We had planned to use a relative risk reduction of 20%, but the distance between the accrued information and the required information was too large, and the program failed to calculate and draw an interpretable figure. We therefore increased the relative risk reduction to 25%. We included trials with zero serious adverse events by substituting zero with a constant of 0.5 (Jacobi-Polishook 2009; Wolraich 2001). We calculated the DARIS on the basis of serious adverse events in the control group of 2%; a relative risk reduction or increase in the experimental group of 25%; type I error of 5%; type II error of 20% (80% power); and diversity ($D^2$) of 0%. The DARIS was 21,593 participants. The cumulative Z-curve did not cross the conventional or trial sequential monitoring boundaries for benefit, harm, or futility (see Figure 5). As only less than 7% of the DARIS was accrued, risks of random type II error cannot be excluded. The Trial Sequential Analysis-adjusted intervention effect was RR 0.91 (CI 0.02 to 33.2).

## Secondary outcomes

### Non-serious adverse events

We were able to combine data on non-serious adverse events from 26 parallel-group trials and 67 cross-over trials in a meta-analysis. The evidence was assessed to be of very low quality (see GRADE assessment below). Therefore, we cannot exclude that harms may be worse than reported.

*Parallel-group trials and cross-over trials (first period data only)*

Overall adverse events

Participants receiving methylphenidate were significantly more likely to experience non-serious adverse events overall (RR 1.29, 95% CI 1.10 to 1.51; $I^2$ = 73%; 21 trials, 3132 participants; Analysis 7.1). Substantial heterogeneity between trials was observed ($Tau^2$ = 0.07; $Chi^2$ = 69.75; df = 19 (P value < 0.00001); $I^2$ = 73%). However, this heterogeneity did not appear to be related to dose, as no differences were reported between low-dose and high-dose methylphenidate trials (test for subgroup differences: $Chi^2$ = 1.11; df = 2 (P value = 0.57); $I^2$ = 0%; Analysis 7.2).

Non-serious adverse events included those affecting the nervous system (Analysis 7.3), as well as the digestive (Analysis 7.4), urinary (no data), circulatory and respiratory (Analysis 7.5), reproductive (no data), skeletal and muscular (Analysis 7.6), and immune systems (Analysis 7.7). Other reported adverse events included physical differences in height (Analysis 7.8), weight (Analysis 7.9), body mass index (BMI) (Analysis 7.10), vital signs (Analysis 7.11), and several less common events (Analysis 7.12).

Compared with those in the control group, participants in the methylphenidate group were more likely to:

1. report trouble sleeping or sleep problems (RR 1.60, 95% CI 1.15 to 2.23; $I^2$ = 0%; 13 trials, 2416 participants; Analysis 7.3);
2. report a decrease in appetite (RR 3.66, 95% CI 2.56 to 5.23; $I^2$ = 28%; 16 trials, 2962 participants; Analysis 7.4) and a decrease in weight (RR 3.89, 95% CI 1.43 to 10.59; $I^2$ = 0%; 6 trials, 859 participants; Analysis 7.4);
3. weigh significantly less (SMD -1.12, 95% CI -1.55 to -0.70; $I^2$ = 83%; 5 trials, 805 participants; Analysis 7.9);
4. have a lower body mass index (BMI) (MD -0.60, 95% CI -0.84 to -0.36; 1 trial, 215 participants; Analysis 7.10); and
5. have a higher pulse (MD 3.41, 95% CI 0.87 to 5.94; $I^2$ = 70%; 8 trials, 1240 participants; Analysis 7.11).

*Cross-over trials (endpoint data)*

Overall adverse events

Significantly more adverse events were reported in the methylphenidate group (RR 1.33, 95% CI 1.11 to 1.58; $I^2$ = 18%; 21 trials, 2072 participants; Analysis 8.1). In addition, differences were noted in the numbers of events reported in trials of low doses of methylphenidate compared with trials of high doses of methylphenidate (test for subgroup differences: $Chi^2$ = 5.68, df = 2; P value = 0.06, $I^2$ = 64.8%; Analysis 8.2).

Categories of non-serious adverse events included those affecting the nervous system (Analysis 8.3), as well as the digestive (Analysis 8.4), urinary (Analysis 8.5), skeletal and muscular (Analysis 8.6), and immune systems (Analysis 8.7), and skin (Analysis 8.8). Other reported adverse events included physical differences in vital signs (Analysis 8.9), height (Analysis 8.10) and weight (Analysis 8.11).

Compared with the control group, participants in the methylphenidate group were less likely to report:

1. anger (RR 0.45, 95% CI 0.26 to 0.77; $I^2$ = 0%; 3 trials, 264 participants; Analysis 8.3);
2. behavioural complaints (RR 0.55, 95% CI 0.35 to 0.86; 1 trial, 82 participants; Analysis 8.3); and

3. an increase in appetite (RR 0.20, 95% CI 0.08 to 0.50; 1 trial, 136 participants; Analysis 8.4).

However, they were more likely to report:

1. compulsive acts (RR 2.57, 95% CI 1.45 to 4.56; 1 trial, 90 participants; Analysis 8.3);
2. daydreaming (RR 0.66, 95% CI 0.44 to 0.98; I² = 0%; 3 trials, 222 participants; Analysis 8.3);
3. headache (RR 1.21, 95% CI 1.01 to 1.45; I² = 0%; 37 trials, 3752 participants; Analysis 8.3);
4. insomnia or sleep problems (RR 1.57, 95% CI 1.20 to 2.06; I² = 47%; 31 trials, 3270 participants; Analysis 8.3);
5. being overly meticulous (RR 40.77, 95% CI 2.35 to 706.72; 1 trial, 96 participants; Analysis 8.3);
6. obsessive thinking (RR 2.35, 95% CI 1.53 to 3.62; 1 trial, 90 participants; Analysis 8.3);
7. tics or nervous movements (RR 1.33, 95% CI 1.03 to 1.72; I² = 10%; 19 trials, 1403 participants) (Analysis 8.3);
8. a decrease in appetite (RR 3.04, 95% CI 2.35 to 3.94; I² = 40%; 35 trials, 3862 participants; Analysis 8.4);
9. stomachache (RR 1.61, 95% CI 1.27 to 2.04; I² = 22%; 33 trials, 3777 participants; Analysis 8.4);
10. somatic complaints (MD 0.85, 95% CI 0.79 to 0.91; 1 trial, 82 participants; Analysis 8.6); and
11. higher pulse/heart rate (MD 5.06, 95% CI 2.88 to 7.24; I² = 57%; 14 trials, 939 participants; Analysis 8.9).

*Trial Sequential Analysis*

We conducted a Trial Sequential Analysis on the 'total non-serious adverse events' outcome involving 21 parallel-group trials. We included one trial with zero non-serious adverse events by substituting zero with a constant of 0.5 (Jacobi-Polishook 2009). We calculated the DARIS on the basis of adverse events in the control group of 47%; relative risk reduction in the intervention group of 20%; type I error of 5%; type II error of 20% (80% power); and diversity (D-square) of 79%. The DARIS was 4133 participants. The cumulative Z-curve (blue line) crossed the trial sequential monitoring boundaries for harm (red inward sloping line) after the 7th trial, and again after the 17th trial (Figure 6). Accordingly, risk of random error in the finding can be excluded according to the Lan-DeMetz-O'Brien-Fleming monitoring boundary. Trial Sequential Analysis-adjusted intervention effect was RR 1.29 (CI 1.06 to 1.56).

**General behaviour**

We were able to include in our analyses data on general behaviour from 7 parallel-group trials and from 19 cross-over trials. The evidence was assessed to be of very low quality (see GRADE assessment below).

*Teacher-rated general behaviour*

Parallel-group trials and cross-over trials (first period data only)

Meta-analysis suggested that methylphenidate significantly reduced teacher-rated general behaviour compared with placebo (SMD -0.87, 95% CI -1.04 to -0.71; I² = 0%; 5 trials, 668 participants; Analysis 9.1). The SMD effect of -0.87 for general behaviour corresponds to an MD of 5.0 points on the CGI (Conners 1998a). However, the evidence was assessed to be of very low quality. All five trials were at high risk of bias (Analysis 9.1). Neither type of scale (Analysis 9.2) nor dose (Analysis 9.3) seemed to significantly influence the intervention effect. We were not able to test for subgroup differences according to duration, as all trials were of short duration, that is, less than six months (Analysis 9.4), or according to trial design, as all trials in the analysis were parallel-group trials (Analysis 9.5).

Cross-over trials (endpoint data)

Meta-analysis suggested that methylphenidate significantly reduced teacher-rated general behaviour compared with placebo (SMD -0.69, 95% CI -0.78 to -0.60; I² = 0%; 16 trials, 2014 participants). The intervention effect was not influenced by the dose of methylphenidate (Analysis 9.6). However, the evidence was assessed to be of very low quality. All 16 trials were at high risk of bias (Analysis 9.7).

Parallel-group trials and cross-over trials (endpoint data)

We observed comparable findings when combining data from parallel-group trials with endpoint data from cross-over trials (SMD -0.79, 95% CI -0.88 to -0.70; I² = 0%; 21 trials, 1976 participants; Analysis 9.8).

*Independent assessor-rated general behaviour*

We found no parallel-group trials that provided data on independent assessor-rated general behaviour. However, for cross-over trials, methylphenidate significantly reduced independent assessor-rated general behaviour symptoms compared with placebo (SMD -0.60, 95% CI -0.75 to -0.46; I² = 32%; 8 trials, 1241 participants; Analysis 10.1). All trials were at high risk of bias (Analysis 10.2). We were not able to test for subgroup differences based on trial design, as all trials in the analysis were cross-over trials (Analysis 10.3).

*Parent-rated general behaviour*

Parallel-group trials and cross-over trials (first period data only)

Meta-analysis suggested that methylphenidate significantly reduced parent-rated general behaviour compared with placebo (SMD -0.53, 95% CI -0.78 to -0.27; I² = 42%; 6 trials, 670 participants; Analysis 11.1). All trials were deemed to have high risk of bias (Analysis 11.2). Furthermore, the intervention effect was significantly influenced by the type of scale (test for subgroup differences: Chi² = 8.52; df = 3 (P value = 0.04); I² = 64.8%; Analysis 11.3). However, no evidence was found to suggest that trial design influenced the intervention effect (Analysis 11.4). We were not able to test for subgroup differences according to duration, as all trials were of short duration, that is, less than six months (Analysis 11.5), or according to dose, as no low-dose methylphenidate trials were conducted (Analysis 11.6).

Cross-over trials (endpoint data)

Meta-analysis suggested that methylphenidate significantly reduced parent-rated general behaviour compared with placebo (SMD -0.75, 95% CI -0.93 to -0.56; I² = 7%; 6 trials, 550 participants; Analysis 11.7). The effect was not significantly influenced by the dose of methylphenidate (Analysis 11.7). All trials were at high risk of bias (Analysis 11.8).

Parallel-group trials and cross-over trials (endpoint data)

We observed comparable findings when combining data from parallel-group trials with endpoint data from cross-over trials (SMD -0.68, 95% CI -0.86 to -0.50; I² = 39%; 12 trials, 1054 participants; Analysis 11.9).

*Additional subgroup analyses*

We found significant differences between raters, with a higher intervention effect for teacher-rated trials (SMD -0.87, 95% CI -1.04 to -0.71, I² = 0%; 5 trials, 668 participants) compared with parent-rated trials (SMD -0.53, 95% CI -0.78 to -0.27; I² = 42%; 6 trials, 670 participants) (test for subgroup differences: Chi² = 5.10, df = 1 (P value = 0.02), I² = 80.4%; Analysis 12.1).

We found no evidence that comorbidity influences the intervention effect (Analysis 12.2), and we found no evidence of a 'carry-over effect' in the cross-over trials (Analysis 12.3).

No data were available for subgroup analyses by age, sex or type of ADHD.

**Quality of life**

We could include data on quality of life from only three parallel-group trials in our analyses. The evidence was assessed to be of very low quality (see GRADE assessment below).

Meta-analysis suggested that methylphenidate significantly improved quality of life compared with placebo (SMD 0.61, 95% CI 0.42 to 0.80; I² = 0%; 3 trials, 514 participants), and no evidence indicated that the type of rating scale - all of which were parent- or clinician-rated - influenced the effect of the intervention (Analysis 13.1). The SMD of 0.61 for quality of life corresponds to an MD of 8.0 (95% CI 5.49 to 10.46) on the Child Health Questionnaire (CHQ; Landgraf 1998), which ranges from 0 to 100 points. All trials were at high risk of bias.

# Discussion

## Summary of main results

We included 38 parallel-group trials and 147 cross-over trials in this review. Altogether, these trials randomised more than 12,000 participants, and were reported in 449 publications. The majority compared methylphenidate with placebo in short-term trials less than six months duration. The average trial duration in the 38 parallel trials was 75 days. Most were conducted in out-patient clinics in high income countries, particularly the USA. Participants' ages ranged from 3 to 18 years across most studies (in two studies ages ranged from 3 to 21 years (Green 2011; Szobot 2008). Both boys and girls were recruited, in a ratio of 5:1 respectively.

All included trials were judged to be at high risk of bias. This raises important concerns, which are discussed following a summary of the results.

The two primary outcomes of this review were ADHD symptoms (with teacher-rated outcomes taking precedence over outcomes reported by parents or independent raters), and number of serious adverse events. Secondary outcomes were non-serious adverse events, general behaviour in school and at home, and quality of life.

### *Primary outcomes*

#### ADHD symptoms

A meta-analysis of data from parallel-group trials combined with data from the first period of cross-over trials suggests that methylphenidate may improve ADHD symptoms as reported by teachers (SMD -0.77, 95% CI -0.90 to -0.64; I² = 37%; 19 trials, 1698 participants; Analysis 1.1). This corresponds to a MD of -9.6 (95% CI -13.75 to -6.38) on the ADHD-RS (DuPaul 1991a), which ranges from 0 to 72. Clinically, this represents a modest improvement in ADHD symptoms.

Subgroup analyses revealed no differences in the effects of methylphenidate based on age, comorbidity or subtypes of ADHD, though the paucity of trials meant we lacked the power to investigate these thoroughly. The quality of the evidence was judged to be ‘very low’ (see Quality of the evidence).

#### Serious adverse events

Methylphenidate does not appear to be associated with an increased occurrence of serious adverse events. However, data for this outcome were only available in 9 of the 185 included trials (4.9%) and the quality of the underpinning evidence was judged to be ‘very low’ (see Quality of the evidence).

### *Secondary outcomes*

#### Non-serious adverse events

Amongst those in the experimental groups, 526 per 1000 (range 448 to 615) experienced non-serious adverse events, compared with 408 per 1000 of those in the control group. This equates to a 29% increase in the overall risk of any non-serious adverse events (RR 1.29, 95% CI 1.10 to 1.51; I² = 73%; 21 trials, 3132 participants; very low-quality evidence; Analysis 7.1). The most common non-serious adverse events were sleep problems and decreased appetite. Children in the methylphenidate group were at 60% greater risk for trouble sleeping/sleep problems (RR 1.60, 95% CI 1.15 to 2.23; I² = 0%; 13 trials, 2416 participants; Analysis 7.3.18 in Analysis 7.3), and 266% greater risk for reduced appetite (RR 3.66, 95% CI 2.56 to 5.23; I² = 28%; 16 trials, 2962 participants; Analysis 7.4.1 in Analysis 7.4) than children in the control group.

The overall quality of the evidence for this outcome was also judged to be 'very low', and as a result, we are uncertain of the magnitude of the harmful effects. Further, for methodological reasons, we used only dichotomous outcomes reflecting the number of participants affected by the event per the total number of participants. As most participants reported more than one adverse event, the actual increase in risk of non-serious adverse events may well be higher than the 29% calculated.

### General behaviour

Meta-analyses of data from five parallel-group trials indicated that methylphenidate was associated with a significant improvement in children's general behaviour, as reported by teachers (SMD -0.87, 95% CI -1.04 to -0.71; $I^2$ = 0%; 668 participants; Analysis 9.1). This effect corresponds to an MD of 5.0 points on the CGI (Conners 1998a). We could find no references describing a MIREDIF on this scale (range 0 to 30 points), and therefore cannot state anything about the clinical significance of this result. Comparable findings emerged from meta-analyses of cross-over trials (endpoint data) as reported by teachers, and from meta-analyses of eight cross-over trials (endpoint data) as rated by independent assessors. This evidence was judged also to be of 'very low' quality (see Quality of the evidence).

### Quality of life

Changes in children's quality of life were assessed in just three trials (n = 514), each of which used a different scale. Measures were scored by parents or clinicians, rather than children. The result (SMD 0.61, 95% CI 0.42 to 0.80; $I^2$ = 0%; Analysis 13.1) is equivalent to a MD of 8.0 points (95% CI 5.49 to 10.46) on the CHQ (Landgraf 1998), a change estimated to represent a clinically important improvement on this scale, which ranges from 0 to 100. The quality of the evidence was judged to be 'very low' (see Quality of the evidence).

The very low quality of the evidence, as assessed using the GRADE approach, undermines the confidence that can be placed in the magnitude of any effect. In particular, the prevalence of non-serious adverse events raises questions about the effectiveness of blinding in these trials. If blinding was broken in just 20% or 30% of patients given methylphenidate, the resulting bias might well account for the small but statistical significant findings concerning the possible benefits of methylphenidate.

## Overall completeness and applicability of evidence

This review highlights two major issues concerning the overall completeness and applicability of the evidence of the benefits and harms of methylphenidate for children with ADHD: the dearth of trials conducted in children and adolescents in low- and middle-income countries, and the lack of follow-up beyond six months. Here, we focus on the impact on the applicability of findings of decisions taken as part of this review (choice of rater for assessing change in ADHD symptoms and quality of life, choice of dose and diagnosis), together with issues relating to rating scales, diagnostic criteria, choice of comparators and adverse events.

### *ADHD symptoms - choice of teacher report*

We chose to use teacher-rated outcomes as the primary measure for both ADHD symptoms and general behaviour, although a number of trials used or relied on parent reports. Some researchers have argued that parent evaluations of ADHD symptoms may not be as reliable as those of other raters such as teachers of pre-school children (Murray 2007) or college students (Lavigne 2012). For example, Caye 2013 suggests inconsistency in ratings between parents, and in the MTA trial, information provided by parents was not always thought to be strong (Efstratopoulou 2013). We tested the robustness of our decision by conducting subgroup analyses and found no significant differences between this score and those of other raters.

Importantly, we do not really know what a lower score on an ADHD symptom scale (like that reported in this review) means for a child's quality of life and ability to live, learn and function with other people.

### *Short-term versus long-term effects*

Based on a subgroup analysis comparing 18 short-term trials (≤ six months) with a single long-term trial (> six months), we found that the treatment effect for teacher-rated ADHD symptoms decreased over time (test for subgroup differences: P value = 0.02). This was not the case for independent assessor- and parent-rated ADHD symptoms, for which no significant differences between short-term and long-term duration were found (P value = 0.09 and 0.53, respectively), but here the power of the subgroup analysis was limited.

We identified no trial that examined the effects of more extended exposure on children's general behaviour. Overall, evidence on the long-term effects of methylphenidate for children and young people with ADHD is lacking, and it is possible that when used for longer periods, any beneficial effects may be diminished or offset by an increase in the risk of harm (Light 2015). Decisions to initiate and persist with treatment will need to weigh potential improvement in ADHD symptoms against adverse events, such as lack of sleep, since this may impact effects on quality of life and learning abilities. This review indicates that these important issues have not been studied sufficiently.

### *Quality of life*

ADHD can exert a significant, negative impact on children's quality of life, broadly defined. Yet only 7 of the 185 included trials measured quality of life in relation both to ADHD and life in general, and it was only possible to synthesize data from three of these trials. In each case the assessments were made by parents, teachers or independent assessors, rather than by children themselves. These external assessors observed small beneficial effects of methylphenidate on quality of life. Children might well have had different views on their own quality of life, and the failure to include child-reported ratings of quality of life is a significant limitation on the completeness of the evidence. Furthermore, observations of quality of life reported by parents, teachers and independent assessors may be subject to both systematic and random errors.

### *Dose – choice of moderate/high dose*

For children weighing 25 kg or less, the maximum recommended dose is 30 mg/d compared to 60 mg/d for children weighing more than 25 kg. After careful consideration, we renamed the high-dose group as 'moderate/high' dose because doses are not always 'high' in heavier children.

Guidelines from the National Institute for Health and Care Excellence (NICE) recommend that methylphenidate can be increased to 0.7 mg/kg per dose up to three times a day, or a total daily dose of 2.1 mg/kg/d. European guidelines recommend that dosage should begin at a low level of 0.2 mg/kg per dose up to three times a day and should increase according to response, to a ceiling of 0.7 mg/kg per dose (up to three times a day), or a total daily dose of 60 mg/d.

In the parallel-group trials included in this review, the mean dose of extended-release methylphenidate was 41.0 mg/d, and the mean dose of immediate-release methylphenidate was 23.1 mg/d. In the cross-over trials included in this review, the mean reported total daily dose of immediate-release methylphenidate was 25 mg/d and extended-release methylphenidate 36 mg/d.

With average doses ranging between 23.1 mg/d and 41.0 mg/d, our cutoff of 20 mg/d seems low. However, many of the included trials were short-term trials, involving medication-naive children who consequently received lower doses. Furthermore, many of the cross-over trials used only morning and midday doses to achieve a cross-over for trial purposes, with no afternoon dose given. However, extended-release methylphenidate is designed to reduce symptoms in the late afternoon too, so the average expected daily dose would be higher.

We performed subgroup analyses to test differences in the estimate of effect based on differences in dosage. These analyses revealed no differences between low doses (≤ 20 mg/d) and moderate/high doses (> 20 mg/d) of methylphenidate. Given the many adverse events that can result when this medication is used, evidence suggests that higher doses may not be needed.

### *Rating scales*

This review included trials from several countries conducted between 1981 and 2014. Pioneers in ADHD research conduct trials in different countries, and psychometric instruments change with trends over time; this is reflected in the variety of rating scales used by investigators in the included trials. Scales based on the diagnostic criteria of the DSM and the ICD measure slightly different constructs. We found significant differences between scales measuring ADHD symptoms, but not between scales measuring general behaviour; we found fewer differences when we performed sensitivity analyses in which we pooled subgroups of scales measuring the same ADHD subtype (e.g. scales measuring the inattentive subtype). All trials using subjective rating scales as proxy measures of outcomes are affected by these problems.

### *Diagnostic criteria*

The diagnostic criterion as regards the age by which ADHD symptoms should first be observed has been much debated ( APA 2013; Todd 2008). As regards DSM-IV age of onset (APA 1994), trials have found no differences in phenotype of neuropsychological impairment, course or treatment response, whether children were diagnosed before or after seven years of age (Kieling 2010). By limiting age of onset to six years or younger, the ICD-10 criteria for hyperkinetic disorder may under-identify children with persistent ADHD symptoms and related impairment (Lahey 2006). In addition, extending age of onset is not implicated in prevalence changes (Polanczyk 2010). It is important to highlight that age of onset is considered only for diagnostic scales, not for rating scales.

The criteria of both the DSM-IV (APA 1994) and the current DSM-5 (APA 2013) encompass a broader spectrum of children with ADHD when compared with the criteria for hyperkinetic disorder in the ICD-10 (WHO 1992); whilst the criteria are virtually identical (Lee 2008; Tripp 1999), the ICD-10 criteria are more restrictively applied. Nonetheless, all have an equal ability to predict ADHD/hyperkinetic disorder, even in the presence of comorbidity (Schachar 2007). Consequently, we believe that our efficacy results would not be changed by any change in diagnostic criteria.

### *Comparators*

The majority of trials in this review compared methylphenidate with placebo, and we earlier highlighted the problems of threats to blinding in these trials, due to the prevalence of non-serious adverse events of methylphenidate. Trials that assess methylphenidate using an ‘active placebo’ (or 'nocebo tablets' - tablets with a placebo-like substance that causes similar adverse events as in the experimental drug arm), can strengthen double blinding and are recommended (Jakobsen 2013; Jakobsen 2014; Moncrieff 2004). We identified no such trials, and as the use of nocebo tablets in all diseases is ethically questionable, any decision to conduct nocebo tablet controlled trials in children should be deferred pending the results of such trials in adults. If these show that methylphenidate is superior to nocebo in treating ADHD symptoms, a rationale would exist for conducting such trials in children. (If another rationale could be mounted, nocebo controlled trials in children would not be ethically questionable, but currently no such case is evident to us).

### *Adverse events*

Methylphenidate non-responders, placebo responders and/or participants with methylphenidate adverse events before randomisation were excluded in 10 parallel-group trials and in 49 cross-over trials. The intervention effect of methylphenidate in these trials was compared with that in the remaining trials in subgroup analyses (Analysis 1.7; Analysis 2.5; Analysis 3.6), which found no differences in terms of the intervention effect of methylphenidate - a surprising finding. However, some of our included trials involved participants who were not medication naive before randomisation, which may have exaggerated the benefits of methylphenidate. They might have detected the physiological effects (for example, improved concentration or adverse events such as appetite suppression) through prior exposure to the effects of methylphenidate. To investigate this,

we performed post hoc subgroup analyses and found that effects of methylphenidate were different in trials involving medication-naive participants (> 80% of included participants were medication naive) than in trials involving participants already taking methylphenidate before randomisation (< 20% of included participants were medication naive) for teacher-rated ADHD symptoms (P value = 0.04), but not for parent-rated ADHD symptoms (P value = 0.52). One might expect the issue of prior exposure to be of greatest concern in cross-over trials. However, we found no differences between parallel-group trials and cross-over trials in both ADHD teacher-rated and parent-rated outcomes. Consequently, we believe that prior exposure is not a major concern when effects of methylphenidate are assessed.

We are currently preparing a second systematic review for the purpose of assessing harms of methylphenidate in observational trials with a duration of up to 36 months (Storebø in press). Preliminary results from this review show a small proportion of serious adverse events reported after treatment with methylphenidate, but one case control trial highlights the risk of sudden death for adolescents (Gould 2009). Just over a quarter of children appear to experience non-serious adverse events after methylphenidate treatment.

Many claims have been made about significant increases in global rates of methylphenidate prescribing; this drug usually is prescribed for long-term use and seldom with medication-free periods. However, a recent paper reports that children in primary care in the UK did not continue methylphenidate treatment for longer than six months (Raman 2015). Furthermore, the incidence of ADHD diagnoses in the UK fell between 1998 and 2010 (Holden 2013). In the USA, however, almost 70% of children with ADHD, estimated at 6.4 million children, take medication (Visser 2014). This might mean that clinicians in the UK are more cautious about using methylphenidate, while US clinicians assume that evidence for the safe use of methylphenidate is sound.

Our assessment of the evidence does not preclude that individual patients may benefit from intervention with methylphenidate. However, despite more than 50 years of research in this field, we do not yet know how to identify those patients that may obtain more benefits than harms. Individual patient data meta-analyses are needed to try to identify such patient characteristics.

### Quality of the evidence

As assessed by the GRADE approach, the overall quality of evidence in this review is 'very low' because of high risk of bias (including loss of blinding (explained below) and outcome reporting bias), inconsistency, and indirectness; this led to uncertainty in the robustness of our estimates. We rated the risk of outcome reporting bias for adverse events to be high, as we only managed to obtain data on total serious adverse events from 9 of the 185 included trials, and on total non-serious adverse events from 21 of the 185 included trials. We found no evidence for publication bias.

It is likely that the trials initially judged to be at low risk of bias may, in fact, be trials at high risk of bias because methylphenidate gives rise to various prevalent and easily recognisable adverse events, which can lead to loss of blinding and hence can bias the ratings of symptoms, resulting in an overestimation of benefits and an underestimation of harms ( Kjaergard 2001; Savović 2012b; Wood 2008). To ensure adequate blinding, it is therefore important for researchers to use a nocebo ('active placebo') in the control group. As we found no trials employing nocebo tablets in the control group, the extent of this bias cannot be assessed. The fact that the intervention effect of methylphenidate on ADHD symptoms did not differ significantly between trials at low risk of bias compared with trials at high risk of bias may be taken as an indication that deblinding has occurred among former trials.

Also, the average duration of treatment was no longer than about two months. Therefore, little can be concluded about the benefits and harms of methylphenidate used for longer than six months.

### Potential biases in the review process

The present systematic review has many strengths. We developed a protocol for this review according to instructions provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Our protocol was published before we embarked on the review itself. We conducted extensive searches of relevant databases, and we requested published and unpublished data from pharmaceutical companies manufacturing methylphenidate, including Shire, Medice (represented in Denmark by HB Pharma), Janssen-Cilag and Novartis. Two review authors, working independently, selected trials for inclusion and extracted data. Disagreements were resolved by discussion with team members. We assessed risk of bias in all trials according to the recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We conducted Trial Sequential Analyses to control the risk of type I errors and to estimate how far we were from obtaining the DARIS to detect or reject a certain plausible intervention effect. In the meta-analyses on non-serious adverse events, the Trial Sequential Analysis showed that observed intervention effects were not likely to be due to type I error and confirmed that sufficient data had been obtained.

We excluded 78 trials described in 88 reports, which assessed the effects of methylphenidate on specialised outcomes (e.g. experimental/neurocognitive/functional outcomes) in children or adolescents with ADHD (see Characteristics of excluded studies). This raises the issue of bias in our review process as we did not write to these authors asking whether they collected data on other outcomes. This potential bias, however, is not likely to change our conclusions. Another limitation of this review is that we did not search the Food and Drug Administration (FDA) and European Medicines Agency (EMA) homepages for unpublished data (Schroll 2015). However, it is also unlikely that these searches would have changed our results.

### Agreements and disagreements with other studies or reviews

Over the past 15 years, several reviews investigating the efficacy of methylphenidate for ADHD (with or without meta-analyses) have been published. Some 15 reviews have pooled results derived from ADHD rating scales on the efficacy of

methylphenidate treatment for children and adolescents with ADHD (Bloch 2009; Charach 2011; Charach 2013; Faraone 2002; Faraone 2006; Faraone 2009; Faraone 2010; Hanwella 2011; Kambeitz 2014; King 2006; Maia 2014; Punja 2013; Reichow 2013; Schachter 2001; Van der Oord 2008). Each of these reviews, however, has several shortcomings and these are described in detail in the subsection Why it is important to do this review. The most important concerns are that none of these reviews are based on a pre-published protocol, and most assessed neither the risk of bias of included trials nor adverse events. Moreover, none of these reviews considered the risk of random errors. Therefore, their interpretation of findings is unlikely to have taken into account the poor reporting of adverse events, the impact of combining data from small trial samples, or the impact of risk of bias on their analyses; information about adverse events is also missing from several RCTs.

A recent Cochrane systematic review evaluated the effects of methylphenidate in adults with ADHD (Epstein 2014). The effect sizes across the different assessments of symptoms were similar to those found in our analyses (SMD 0.60). The authors noted that data on adverse events were limited by the short duration of the included trials (Epstein 2014). Despite the similar effects of methylphenidate on symptoms observed in our reviews, readers will notice that we have judged the quality of evidence in our review, as well as that in Epstein 2014 (Storebø 2015b [pers comm]), to be lower than Epstein and colleagues.

In order to address uncertainties over the frequency and severity of long-term adverse events of methylphenidate, we are currently preparing a second systematic review of observational studies (Storebø in press), which will investigate the long-term harms of methylphenidate as reported by non-randomised studies with a duration of up to 36 months. We hope this will help us to understand the long-term safety profile of the drug.

# Authors' conclusions

## Implications for practice

Methylphenidate may improve ADHD symptoms, general behaviour and quality of life in children and adolescents aged 18 years and younger with ADHD. We rated the evidence to be of very low quality and, as a result, we cannot be certain about the magnitude of the effects from the meta-analyses. The evidence is limited by serious risk of bias in the included trials, under-reporting of relevant outcome data, and a high level of statistical variation between the results of the trials. There is also very low quality evidence that methylphenidate causes numerous adverse events. The risk of serious adverse events seems low, but data were available from only 9 of the 185 included trials. It is also problematic that only 93 of the 185 included trials reported on specific and overall non-serious adverse events. Accordingly, we cannot rule out the possibility that non-serious harms are more prevalent than reported in our review.

If methylphenidate treatment is considered, clinicians might need to use it for short periods, with careful monitoring of both benefits and harms, and cease its use if no evidence of clear improvement of symptoms is noted, or if harmful effects appear.

## Implications for research

To assess whether any benefits are provided by methylphenidate, large, randomised, nocebo tablet ('active placebo') controlled trials are needed to compare the drug with a nocebo tablet, if deblinding can be excluded. A problem with many pharmacological trials is that participants in the experimental drug group experience adverse events that compromise the blinding, as fewer adverse events occur in participants in the placebo group. However, given the ethical dilemmas regarding the use of nocebo tablets in children, such trials should be conducted first in adults with ADHD, unless one can provide a rationale to justify nocebo controlled trials in children (Moncrieff 2004; Požgain 2014). Nocebo controlled trials in adults demonstrating that methylphenidate is superior to nocebo in treating ADHD symptoms would provide a rationale for conducting such trials in children. In addition, such trials ought to be designed according to the SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) guidelines (Chan 2013), and reported in keeping with the CONSORT (Consolidated Standards of Reporting Trials) standards Moher 2010).

The prevalent use of cross-over trials needs to be reconsidered because they usually provide only short-term interventions, and this can limit the assessment of benefits and harms. However, we were not able to identify major differences when comparing parallel-group trials with cross-over trials.

Future trials ought to publish depersonalised individual participant data and should report all outcomes, including adverse events, to ensure that future systematic reviews and meta-analyses can access and use individual participant data. Only through meta-analyses will we be able to assess differences between intervention effects according to age, sex, comorbidity, type of ADHD and dose.

Reviews show that many different rating scales are used for children with ADHD. Consistent use of good validated scales is needed, as is a country-wide adverse events reporting system, such as the FDA, to increase awareness of adverse events.

This review highlights the need for long-term, high-quality trials with low risk of bias and with sufficient numbers of participants, investigating the benefits and harms of methylphenidate treatment versus placebo for children and adolescents with ADHD. Pre-published protocols could help reduce inconsistent measurement of benefits and harms caused by the use of many different rating scales and by lack of assessment of adverse events. In addition, the findings in this review clearly show the urgent need for large RCTs to investigate the efficacy of non-pharmacological treatments.

As with RCTs, systematic reviews of RCTs assess average effects in groups of individuals. Such average effects may comprise strong benefits for a single participant or a few participants and no effect or negative effects for others. Despite more than 50 years of research in this field, we have no knowledge on how to identify patients that may obtain more benefits

than harms. Individual patient data meta-analyses are needed in order to identify such patient characteristics. Therefore, it would be extremely helpful for review authors to gain full access to anonymised individual participant data for inclusion in meta-analyses examining these data (Gluud 2015b). Particular patient subgroups may benefit from an intervention if those with reduced rates of adverse events can be identified.

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## Contributions of authors

OJS has overall responsibility for the review.

OJS, MS, SR, CGr, KBR, ES and CGl contributed to writing the protocol.

KBR developed the search strategy.

OJS, ER, HBK, TDN, MS, MH, SR, FLM, BF and KBR selected the studies.

OJS, ER, HBK, TDN, MS, MH, SR, CGr, FLM, CMM, DG, KBR, DG, MZ, RK and ES extracted data and evaluated bias.

OJS and CGl developed the analytical strategy.

OJS, ER, HBK, MH, FLM and CRMM entered data into RevMan.

OJS, ER, HBK, MH, FLM and CRMM conducted the statistical analysis.

All review authors participated in discussion and writing of the final review.

## Declarations of interest

Ole Jakob Storebø - none known.
Erica Ramstad - none known.
Helle B. Krogh - none known.
Trine Danvad Nilausen - none known.
Maria Skoog - none known.
Mathilde Holmskov - none known.

Susanne Rosendal - none known.
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Frederik Løgstrup Magnusson - none known.
Carlos R Moreira-Maia - receives financial research support from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). CRMM has served as speaker for Novartis, has developed educational materials for Novartis, has received travel awards from the Health Technology Assessment Institute (IATS) and the Universidade Federal do Rio Grande do Sul (UFRGS), and has received travel and registration support to attend the 5th World Congress on ADHD from the World Federation of ADHD.
Donna Gillies - is an Editor with the Cochrane Developmental, Psychosocial and Learning Problems Group.
Kirsten Buch Rasmussen - none known.
Dorothy Gauci - none known.
Morris Zwi - sits on the Paediatric Medicines Expert Advisory Group at the Medicines and Healthcare Products Regulatory Agency, which considers applications regarding licensing of paediatric medicines. Payment for MZ's attendance at this meeting goes to his National Health Service (NHS) organisation.
Richard Kirubakaran - is currently employed by Cochrane South Asia. His salary is funded by the Effective Healthcare Research Consortium (EHCRC) for the Department for International Development (DFID), UK.
Bente Forsbøl - none known.
Erik Simonsen - none known.
Christian Gluud - none known.

## Differences between protocol and review

**1. Methods section. Criteria for considering studies for this review. Types of studies.**

We decided to split the review into two systematic reviews. The present review deals with benefits and harms of methylphenidate as reported by RCTs. Another systematic review is being prepared that will assess the risk of harms based on the findings of non-randomised studies.

**2. Methods section. Criteria for considering studies for this review. Types of participants.**

We decided to include trials in which at least 75% of participants were 18 years of age or younger, and the mean age of the trial population was 18 years of age or younger. We included two trials with such participants. The effects of methylphenidate intervention on any outcome did not change when these two trials were removed from the analysis.

We decided to include trials in which at least 75% of participants had a normal intellectual quotient (IQ > 70). We included three trials with such participants. The effects of methylphenidate intervention on any outcome did not change when these three trials were removed from the analysis.

**3. Methods section. Criteria for considering studies for this review. Types of outcome measures.**

Duration of studies. We changed the subdivision of duration from short term (≤ 6 months), medium term (6 to 12 months) and long term (> 12 months) to short term (≤ 6 months) and long term (> 6 months) because no trials had a duration of between 6 and 12 months. Only one trial (Jensen 1999 (MTA)) provided data on a duration longer than six months (14 months). This change regarding duration classification was included in analyses of ADHD symptoms and general behaviour.

**4. Methods section. Search methods for identification of studies.**

We did not search for dissertations in WorldCat, Networked Digital Library of Theses and Dissertations, OpenGrey, DART-Europe E-theses Portal and Theses Canada. We did not contact the medical authorities in the European Union for information about beneficial and adverse events. We did not ask for access to security updates and risk management plans of pharmaceutical companies.

**5. Methods section. Data collection and analysis. Selection of studies and data extraction and management.**

More review authors than stated in the protocol screened titles and abstracts, extracted data, entered data into RevMan and conducted statistical analyses in RevMan.

**6. Methods section. Data collection and analysis. Assessment of risk of bias in included studies.**

Vested interests. We did not evaluate what effects might have been seen if the study author had conducted previous trials addressing the same interventions.

**7. Methods section. Data collection and analysis. Measures of treatment effect. Continuous data.**

For the primary outcome of teacher-rated ADHD symptoms, we recalculated the SMD as MD on the ADHD-RS (DuPaul 1991a), to check whether our result exceeded the minimum clinically important difference (MCID; Zhang 2005) for this specific rating scale. This was not stated in the protocol.

For the secondary outcome of quality of life, we recalculated the SMD as MD on the CHQ (Landgraf 1998), to check whether our results exceeded the MCID (Rentz 2005) for this specific rating scale. This was not stated in the protocol.

**8. Methods section. Dealing with missing data.**

We tried to obtain missing data by contacting the authors of the trials that were included in this review. When we were not able to obtain missing data, we conducted analyses using available (incomplete) data. We had intended to assess the impact of missing data by applying intention-to-treat as well as 'best-case scenario' and 'worst-case scenario' analyses. We could

not use 'best-case scenario' and 'worst-case scenario' analyses in our assessment of benefits as there were no dichotomous outcomes. We decided not to use 'best-case scenario' and 'worst-case scenario' analyses in our assessment of adverse events, because we evaluated these analyses to be imprecise due to the high number of trials not reporting adverse events, and due to the high number of dropouts in the trials reporting adverse events. Moreover, we were unable to conduct intention-to-treat analyses for continuous outcomes due to lack of data for imputing means.

**9. Methods section. Data collection and analysis. Assessment of reporting bias.**

We did not compare results extracted from published journal reports versus results obtained from other sources (including correspondences) as a direct test for publication bias.

**10. Methods section. Subgroup analysis and investigation of heterogeneity. Post hoc subgroup analyses.**

1. Types of scales (e.g. Conners' Teacher Rating Scale (CTRS; Conners 1998a) versus Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) Scale (Swanson 2006).
2. Dose of methylphenidate (low dose (≤ 20 mg/d or ≤ 0.6 mg/kg/d) versus moderate/high dose (> 20 mg/d or > 0.6 mg/kg/d)).
3. Duration of treatment (short-term trials (≤ six months) versus long-term trials (> six months)).
4. Trial design (parallel-group trials versus cross-over trials (first period data and endpoint data)).
5. Medication status before randomisation (medication naive (> 80% of included participants were medication naive) versus not medication naive (< 20% of included participants were medication naive)).
6. Risk of bias (trials with low risk of bias versus trials with high risk of bias).
7. Cohort selection bias (trials with cohort selection bias of all participants versus trials without cohort selection bias)

**11. Methods section. Data collection and analysis. Heterogeneity-adjusted required information size and Trial Sequential Analysis.**

We performed a Trial Sequential Analysis on the total number of serious adverse events and on the total number of non-serious adverse events only, as they were the only outcomes with dichotomous data with a substantial number of outcomes. Trial Sequential Analysis can be conducted on individual types of adverse events, but for this, the accrued information would represent a minute fraction of the required information size (RIS). We were not able to conduct a Trial Sequential Analysis for teacher-, independent assessor- or parent-rated outcomes, as the programme can be used only for MDs, not for SMDs.

# Published notes

# Characteristics of studies

## Characteristics of included studies

### *Abikoff 2009*

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| Methods | Eight-week double-blind, randomised, placebo-controlled, cross-over trial with 2 interventions<br>1. OROS methylphenidate<br>2. Placebo |
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| Participants | Number of participants screened: not stated<br>Number of participant included: 19 (15 boys, 4 girls). Participants randomly assigned to 1 of 2 possible drug condition orders<br>Number of participants followed up: 19<br>Number of withdrawals: none<br>Diagnosis of ADHD: DSM-IV (combined (42%), hyperactive-impulsive (0%), inattentive (58%))<br>Age: mean 10.05 years (SD 1.62, range 8 to 13)<br>IQ: mean 107.1 (SD 14.3)<br>Methylphenidate naive: 100%<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: ODD (26.3%), anxiety disorder (10.5%), dysthymic disorder (5.3%), conduct disorder (5.3%)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. DSM-IV criteria for ADHD (combined or inattentive type)<br>2. Meeting dimensional criteria for ADHD symptom severity on Conners' Teacher Rating Scale - Revised, long form, defined as a score ≥ 1.5 SD above age and sex norms<br>3. Impaired Organisational, Time Management and Planning treatment (OTMP), defined by a mean total score ≥ 1 SD below the norm on the Children's Organizational Skills Scale - Parent, and the Children's Organizational Skills Scale - Teacher<br>4. Score ≥ 80 on the Wechsler Abbreviated Scale of Intelligence<br>**Exclusion criteria**<br>1. Diagnosis of autism, major depression, substance abuse, obsessive-compulsive disorder, post-traumatic stress disorder, panic disorder, tic disorders, significant suicidality<br>2. Lifetime history of psychosis or mania<br>3. Learning disability according to a school individualised educational plan<br>4. Taking other CNS medications |
| Interventions | Participants were randomly assigned to 1 of 2 possible orders of OROS methylphenidate and placebo<br>Mean methylphenidate dosage: 48.3 mg (range 18 ± 54 mg); weight-based final OROS methylphenidate dose was 1.3 mg/kg<br>Administration schedule: not stated<br>Duration of each medication condition: 4 weeks: 2 weeks titration and 2 weeks optimal dose<br>Washout before study initiation: 2 days between interventions<br>Titration period: 2 weeks after randomisation<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. Swanson, Nolan and Pelham Scale, Fourth Edition, parent-rated at baseline, after weeks 1 and 2 (during titration) and at end of treatment (4 weeks)<br>2. Swanson, Nolan and Pelham Scale, Fourth Edition, teacher-rated at baseline, after weeks 1 and 2 (during titration) and at end of treatment (4 weeks) |

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| **Notes** | Sample calculation: no<br>Ethics approval: Study protocol was reviewed and approved by the University's institutional review board<br>**Comment from study authors**<br>1. The 4 weeks of OROS methylphenidate treatment was relatively brief, and post-treatment measures were obtained after children had been taking their optimal titration dose for 2 weeks<br>**Key conclusion of study authors**<br>1. OROS methylphenidate reduced children's OTMP deficits, and these improvements were associated with improvement in ADHD symptoms. Some children remained impaired in OTMP even after effective stimulant treatment for ADHD symptoms. These youngsters may require other treatments that target OTMP deficits<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: December 2013. No supplemental information provided |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not stated |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Unclear risk | Double-blind |
| Blinding of outcome assessment (detection bias) | Unclear risk | Double-blind |
| Incomplete outcome data (attrition bias) | Low risk | Post-treatment scores for all 19 study children were obtained from parents. Because 1 child's treatment was delayed and ran beyond the end of the school year, teacher data on 18 youngsters were analysed<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Low risk | No protocol published. All pre-specified outcomes of interest have been reported |
| Vested interest bias | High risk | Investigator-initiated trial funded by a grant from Ortho-McNeil Janssen Scientific Affairs to Dr. Abikoff<br>Conflicts of interest: Drs. Abikoff and Gallagher have a contract with Multi-Health Systems to further develop the Children's Organizational Skills Scale (COSS) used in this study. Dr. Abikoff has served on the ADHD Advisory Board of Shire Pharmaceuticals and of Novartis Pharmaceuticals. Dr. Boorady has served on the ADHD Advisory Board and Speakers' Bureau of Shire Pharmaceuticals. Other study authors report no conflicts of interest |

*Ahmann 1993*

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| **Methods** | Three-week double-blind, placebo-controlled, cross-over trial, in which participants were randomly assigned to<br>1. Methylphenidate (low and high doses; Ritalin)<br>2. Placebo |

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| Participants | Number of participants screened: not stated<br>Number of participants included: 234. Participants were randomly assigned to low-dose methylphenidate (0.3 mg/kg), high-dose methylphenidate (0.5 mg/kg) or placebo<br>Number of participants followed up: 206<br>Number of withdrawals: not stated, but it is described in the text that 4 children experienced severe side effects while taking Ritalin and could not complete the protocol<br>**Regarding the 206 participants**<br>Diagnosis of ADHD: DSM-III-R (subtype not stated)<br>Age: 5 to 15 years<br>IQ: > 70<br>Sex: 161 boys, 45 girls<br>Methylphenidate naive: not stated<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Informed consent from parent<br>2. DSM-III-R diagnosis of ADHD<br>In addition, ≥ 3 of the following criteria had to be met<br>1. Attention score on the ADD-H Comprehensive Teacher Rating Scale: at or below 25th percentile<br>2. Hyperactivity score on the ADD-H Comprehensive Teacher Rating Scale: at or below 25th percentile<br>3. Inattention/Passivity score on Conners' Teacher Rating Scale (28 items): ≥ 2 SD above the mean<br>4. Hyperactivity Index on Conners' Teacher Rating Scale (28 items): ≥ 2 SD above the mean<br>5. Hyperactivity Index on Conners' Parent Rating Scale (48 items): ≥ 2 SD above the mean<br>Children were divided into responders and non-responders based on the following criteria<br>1. Parent reported 1 SD improvement on the Hyperactivity Index of the Conners' Parent Rating Scale (48 items) or gave a positive narrative comment, and<br>2. Teacher reported ≥ 2 of the following<br>a. 10 percentile improvement in Attention Score on the ADD-H Comprehensive Teacher Rating Scale<br>b. 10 percentile improvement in Hyperactivity Score on the ADD-H Comprehensive Teacher Rating Scale<br>c. 1 SD improvement on the Inattention/Passivity Scale of Conners' Teacher Rating Scale (28 items)<br>d. 1 SD improvement on the Hyperactivity Index of Conners' Parent Rating Scale (48 items)<br>e. Positive narrative comment<br>**Exclusion criterion**<br>1. Children with a history of seizures, mental retardation, Tourette's syndrome or other significant neurological history were not eligible for the study |

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| Interventions | Participants were randomly assigned to different orders of low-dose Ritalin (0.3 mg/kg), high-dose Ritalin (0.5 mg/kg) or placebo<br>Administration schedule: 3 times a day<br>Duration of each medication condition: 7 consecutive days<br>Washout before study initiation: not stated<br>Titration period: not stated<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. ADD-H Comprehensive Teacher Rating Scale (24 items): rated each week<br>2. Conners' Teacher Rating Scale (28 items): rated each week<br>3. Conners' Parent Rating Scale (48 items): rated each week<br>**Non-serious adverse events**<br>1. Barkley Side Effects Questionnaire: parent-rated, weekly |
| Notes | Sample calculation: *n*o<br>Ethics approval: yes; protocol was approved by the Institutional Review Board at the Marshfield Medical Center<br>**Key conclusion of study authors**<br>1. The Barkley Side Effects Questionnaire proved to be clinically effective in tracking Ritalin side effects and should be incorporated into the routine evaluation and monitoring of ADHD patients for whom stimulants are prescribed<br>**Comment from review authors**<br>1. Study divided participants into 2 groups: responders and non-responders. 147 children were determined to be Ritalin responders. Both responders and non-responders (n = 206) were included in the analysis of side effects<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: not able to find study authors' contact information; therefore not able to obtain supplemental information regarding study design and data on ADD-H Comprehensive Teacher Rating Scale, Conners' Teacher Rating Scale, Conners' Parent Rating Scale |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomly assigned, but not described how and/or by whom |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | Double-blind trial, identical appearing pills |
| Blinding of outcome assessment (detection bias) | Low risk | Double-blind trial, identical appearing pills |
| Incomplete outcome data (attrition bias) | Low risk | 206 had sufficient data for analyses<br>Selection bias: Participants were divided into responders and non-responders. However, data from this article pertain to side effects only and include both groups |
| Selective reporting (reporting bias) | Unclear risk | Not able to obtain protocol or other information |
| Vested interest bias | Low risk | Study was funded by Marshfield Clinic grants |

### *Armstrong 2012*

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| **Methods** | Two identical, concurrently conducted, phase 4, double-blind, randomised, cross-over, analogue classroom trials with 2 interventions<br>1. OROS methylphenidate<br>2. Placebo<br>**Phases**<br>1. Screening/washout phase: up to 28 days<br>2. Titration: up to 6 weeks<br>3. Double-blind assessment period, with the following subperiods<br>a. Open-label OROS methylphenidate<br>b. School day 1: OROS methylphenidate or placebo<br>c. Open-label OROS methylphenidate: ≥ 7 days<br>d. School day 2: OROS methylphenidate or placebo |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 78 (55 boys, 23 girls)<br>Number of participants followed up: 71<br>Number of withdrawals before randomisation: 7<br>Number of withdrawals after randomisation: 0<br>Diagnosis of ADHD: DSM-IV-TR (combined (81%), hyperactive-impulsive (0%), inattentive (19%))<br>Age: mean 10.1 years (range 9 to 12 years)<br>IQ: > 80<br>Methylphenidate naive: not stated<br>Ethnicity: Caucasian (58%), African American (28%), other (14%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: anxiety (0%), depressive disorders (0%), learning disability (32%)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. 9 to 12 years of age<br>2. DSM-IV-TR diagnosis of ADHD |

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| | 3. Baseline score on ADHD Rating Scale, Fourth Edition, in the 90th percentile or greater relative to the general population of children of the same age and sex<br>4. Participants receiving medication for ADHD at the time of study enrolment exhibited an inadequate response to their then-current stimulant dose and completed a washout equivalent to 5 half-lives of the given medication before completing baseline assessments<br>5. Attendance at regular school<br>6. Ability to read and understand English<br>7. To be eligible for the double-blind, randomised assessment period, participants had to reach their individualised dose of OROS methylphenidate, defined as<br>a. Score on the ADHD Rating Scale, Fourth Editiion (as scored by parent or guardian): ≤ 75th percentile for age and sex<br>b. Score on the ADHD Rating Scale, Fourth Editiion (as scored by parent or guardian): between 75th and 85th percentiles for age and sex after (1) dose decrease for tolerability (1 dose decrease by 18 mg to a minimum of 18 mg/d was allowed) or (2) having reached dosage of 54 mg/d<br>**Exclusion criteria**<br>1. History or current diagnosis of epilepsy, severe anxiety or conduct or psychotic disorders<br>2. Pervasive developmental, eating, obsessive-compulsive, sleep, major depressive, bipolar or chronic tic disorder, substance use disorder<br>3. Personal or family history of Tourette's syndrome<br>4. Known cardiac abnormalities: clinically significant abnormalities in ECG results; family history of sudden death or ventricular arrhythmia<br>5. Inability to take or tolerate OROS methylphenidate<br>6. Allergies to MPH or other ingredients of OROS methylphenidate<br>7. Known gastrointestinal narrowing or significant gastrointestinal problems<br>8. Glaucoma<br>9. Use of medication with CNS effects (excluding bronchodilators)<br>10. Clinically significant laboratory and ECG abnormalities and blood pressure in the 95th percentile or greater for age, sex and height<br>11. Study participants were prohibited from using any caffeine-containing products on study visit days or laboratory assessment days, and were limited to 1 (12-ounce) caffeinated beverage a day during study participation<br>12. Estimated full-scale IQ 80, as measured by the Wechsler Abbreviated Scale of Intelligence<br>13. Scores of ≥ 2 SD less than mean scores for age on the Gray Oral Reading Test (GORT), the Comprehensive Test of Phonological Processing (CTOPP), or the Wechsler Individual Achievement Test - Second Edition (WIAT-II AB13))<br>14. Weight < 3rd percentile for age<br>15. History of hospitalisation for treatment of a mood, anxiety or psychotic disorder<br>16. History of failed response to methylphenidate |
| **Interventions** | Participants were randomly assigned to 1 of 2 possible drug condition orders of OROS methylphenidate and placebo<br>Mean OROS methylphenidate daily dosage: 40.5 mg<br>Administration schedule: once daily (morning)<br>Average duration of OROS methylphenidate treatment: 40 days<br>Duration of placebo intervention: 1 day<br>Washout before study initiation: up to 28 days<br>Medication-free period between interventions: no<br>Titration period: before randomisation, up to 6 weeks<br>Treatment compliance: not stated |

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| Outcomes | **ADHD symptoms**<br>1. Swanson, Kotkin, Atkins, M-Flynn and Pelham Scale, observer-rated, 4 hours post dose (on the 2 laboratory days)<br>**Serious adverse events**<br>1. Serious adverse effects assessed on the 2 laboratory days and during the open-label period<br>**Non-serious adverse events**<br>1. Adverse effects, vital signs and body weight, assessed on the 2 laboratory days |
| Notes | Sample calculation: yes<br>Ethics approval: yes<br>**Key conclusions of study authors**<br>1. Wigal 2011 (Armstrong 2012): OROS methylphenidate dose to reduce core symptoms of ADHD to within the normal range also improved performance on a variety of academic tasks in school-aged children compared with placebo. Reported adverse effects were consistent with those of prior studies<br>2. Armstrong 2012 (Armstrong 2012): Robust treatment effect occurred with OROS methylphenidate; onset was at 1 hour post treatment and persisted for ≥ 12.5 hours after dosing<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; a history of failed response to methylphenidate was an exclusion criterion. Only children demonstrating the required decrease in ADHD symptoms with MPH-OROS within the labelled dosing range were included in the randomised phase of the study. Children who may have required a dose > 54 mg to achieve full therapeutic effect may also have been excluded<br>Any withdrawals due to adverse events: yes (n = 2)<br>Email correspondence with study authors: June 2013 to June 2014. Obtained supplemental efficacy data (Swanson, Kotkit, Agler, M-Flynn and Pelham Scale) and safety data. Awaiting data through the Yale Open Data Access Project |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Wigal 2011; computer-generated randomisation schedule |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | Wigal 2011; blinding of investigators and participants maintained throughout the study |
| Blinding of outcome assessment (detection bias) | Low risk | Wigal 2011; blinding of investigators and participants maintained throughout the study |
| Incomplete outcome data (attrition bias) | Unclear risk | No information on incomplete outcome data<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Low risk | All outcomes reported according to protocol |
| Vested interest bias | High risk | Supported by Ortho-McNeil-Janssen Scientific Affairs, LLC. Phase IV study<br>Conflicts of interest: Several study authors had affiliations with pharmaceutical companies producing methylphenidate |

*Arnold 2004*

| Methods | Seven-centre US study consisting of a 6-week, open-label, dose-titration phase (Part A) and a 2-week, double-blind, randomised, parallel-group, placebo-controlled withdrawal study (Part B) with 2 arms<br>1. Dexmethylphenidate<br>2. Placebo |
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| Participants | Number of patients screened: 116<br><br>**Regarding Part A**<br><br>1. Number of participants included: 89 (72 boys, 17 girls)<br>2. Number of participants followed up: 76<br>3. Number of withdrawals: 13<br>4. DSM-IV diagnosis of ADHD (combined 80%)<br>5. Age range: 6 to 16 years<br>6. IQ: not stated<br>7. Methylphenidate naive: 71.9%<br>8. Ethnicity: not stated<br>9. Country: USA<br>10. Comorbidity: not stated<br>11. Comedication: not stated<br>12. Sociodemographics: not stated<br><br>**Regarding Part B**<br><br>1. Number of participants included: 75 (61 boys, 14 girls)<br>2. Number randomly assigned: methylphenidate 35, placebo 40<br>3. Number followed up in each arm: methylphenidate 34, placebo 39<br>4. Number of withdrawals in each arm: methylphenidate 1, placebo 1<br>5. DSM-IV diagnosis of ADHD (combined (80%), hyperactive-impulsive (0%), inattentive (20%))<br>6. Age range: 6 to 16 years<br>7. IQ: > 70 (mean not stated)<br>8. MPH-naive (methylphenidate 82.9%, placebo 62.5%)<br>9. Ethnicity: Caucasian (methylphenidate 80%, placebo 75%), African American (methylphenidate 14.3%, placebo 12.5%), Hispanic (methylphenidate 5.7%, placebo 12.5%)<br>10. Country: USA<br>11. Setting: out-patient clinic and hospital<br>12. Comorbidity: not stated<br>13. Comedication: antihistamines, non-steroidal anti-inflammatory agents, multi-vitamins, nasal decongestants or other analgesics or antipyretics (methylphenidate 34.3%, placebo 40.0%)<br>14. Sociodemographics: not stated<br><br>No significant differences in baseline demographics were noted between the 2 groups. Thus, slightly more treatment-naive participants were receiving d-MPH than placebo<br><br>**Inclusion criteria**<br><br>1. 6 to 17 years of age<br>2. Enrolled in school<br>3. DSM-IV diagnosis of ADHD, any subtype<br>4. Within 30% of normal body weight<br>5. Able to participate for the full 8 weeks<br><br>**Exclusion criteria**<br><br>1. History or evidence of cardiovascular, renal, respiratory (other than asthma/allergy), endocrine or immune system disease<br>2. History of substance abuse<br>3. Hypersensitivity to d,l-MPH or other stimulants<br>4. Treatment with any investigational drug within 30 days of screening<br>5. Other significant CNS disorders<br>6. Treatment with antidepressants, neuroleptics/antipsychotics, mood stabilisers, anticonvulsants, beta-blockers, alpha-2-agonists, other stimulants, thyroid medications, long-term oral steroids or sedatives/hypnotics<br>7. Concurrent treatment with other psychoactive drug |

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| Interventions | **Part A**<br>Dexmethylphenidate dosage: 2.5 to 10 mg, twice daily depending on individual participants' prior medication experience. Children who had received d,l-MPH began with half their total daily d,l-MPH dose administered as dexmethylphenidate but not more than 20 mg/d; those who had not previously received d,l-MPH started d-MPH at 2.5 mg twice daily<br>Duration of intervention: 6 weeks<br>Treatment compliance: not stated<br>**Part B**<br>Participants were randomly assigned to dexmethylphenidate or placebo<br>Mean methylphenidate dosage: 68.6% of dexmethylphenidate continuers and 79.5% of placebo participants were receiving 20 mg at end of Part B, mean (SD) not stated<br>Administration schedule: 10 mg twice daily. Time points 7 AM to 8 AM and 11:30 AM to 12 PM<br>Duration of intervention: 2 weeks<br>Titration period: 6 weeks, initiated before randomisation<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms (Part B)**<br>1. Swanson, Nolan and Pelham Scale, teacher-rated at baseline and at end of treatment<br>2. Swanson, Nolan and Pelham Scale, parent-rated at baseline and at end of treatment, 3 and 6 hours post dose<br>**Non-serious adverse events (Parts A and B)**<br>1. Monitoring of adverse events and changes from baseline in vital signs (pulse and blood pressure), physical examination and clinical laboratory parameters throughout the study |
| Notes | **Comments from study authors**<br>1. Limitations<br>a. Study design: Treatment effects in such trials may be larger than those seen in unselected populations because, in the randomised withdrawal phase, responders were pre-selected from the open-label titration phase to the drug phase.<br>b. Another possible limitation is the duration of discontinuation (2 weeks)<br>**Key conclusion of study authors**<br>1. Dexmethylphenidate is safe, tolerable and effective, with a 6-hour duration of effect suggested by significant differences from placebo at 6 hours on double-blind discontinuation<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: October 2013. Supplemental information regarding additional information was received. However, study authors advised us to contact the sponsoring drug company for additional information. This process has been difficult, and no further communication was attempted to request additional information |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomisation was central, irrespective of whether the drug was pre-packaged and pre-randomised, or if it was bottled and labelled by an unblinded dispenser who had no contact with participants and kept the other staff blind |
| Allocation concealment (selection bias) | Low risk | Randomisation was central. "In all industry studies I have been involved with, either the drug was pre-packaged and pre-randomized or it was bottled and labeled by an unblinded dispenser who had no contact with patients and kept the other staff blind" |
| Blinding of participants and personnel (performance bias) | Low risk | Double-blind. In Part B, participants/guardians and medical personnel were blinded to the drug. Also, d-methylphenidate was available in tablets, each identical in appearance to a matching placebo. Study drug (or placebo) was dispensed in bottles containing a weekly supply, labelled for use at “Home” and “School”, with the strength designated “A,” “B” or “C” |
| Blinding of outcome assessment (detection bias) | Low risk | Double-blind. In Part B, participants/guardians and medical personnel were blinded to the drug |
| Incomplete outcome data (attrition bias) | Low risk | ITT sample was used in analysis of efficacy parameters: Participants who received dexmethylphenidate and had a Part B baseline efficacy evaluation and ≥ 1 post-baseline assessment |
| Selective reporting (reporting bias) | Low risk | No protocol published. All pre-specified outcomes of interest have been reported |
| Vested interest bias | High risk | Study was supported by the Celgene Corporation<br>Conflicts of interest: Drs. Arnold, Wigal and Bohan received research funding from Celgene for the study reported. Dr. Wigal and Dr. West are on the Advisory Panel and Speakers' Bureau for Novartis. Dr. Arnold and Dr. Bohan are on the Speakers' Bureau for Novartis. Dr. Zeldis is Chief Medical Officer and Vice President of Medical Affairs at the Celgene Corporation |

*Ashare 2010*

| Methods | Three-day, double-blind, randomised, placebo-controlled medication assessment (cross-over) |
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| Participants | Number of patients screened: not stated<br>Number of participants included: 50. Participants were randomly assigned to methylphenidate (low dose, high dose) or placebo<br>Number of participants followed up: 36 (28 boys, 8 girls)<br>Number of withdrawals: 14<br>Diagnosis of ADHD: DSM-IV (combined (61%), hyperactive-impulsive (8%), inattentive (31%))<br>Age: mean 10.5 years (range 9 to 12)<br>IQ: mean 102 (SD 13)<br>Methylphenidate naive: 7 participants<br>Ethnicity: Caucasian (80%), African American (17%), mixed race (3%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder (47%), conduct disorder (17%)<br>Comedication: no<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. DSM-IV diagnosis of ADHD<br>2. 9 to 12 years of age<br>**Exclusion criteria**<br>1. Full-scale IQ < 80<br>2. History of seizures, neurological disorders and other medical problems<br>3. Contraindicating psychostimulant treatment<br>4. Current use of non-ADHD psychotropic medications<br>5. History or concurrent diagnosis of pervasive developmental disorder or psychosis, and sensory problems that would make it difficult to complete the task |
| Interventions | Participants were randomly assigned to 2 doses of long-acting methylphenidate (OROS methylphenidate; Concerta) once a day and placebo<br>1. One (low dose) provided equivalent effects to t.i.d. immediate-release methylphenidate at 0.3 mg/kg dose, producing a total daily dose of 0.9 mg/kg<br>2. The other (high dose) was equivalent to t.i.d. immediate-release methylphenidate 0.6 mg/kg dose, producing a total daily dose of 1.8 mg/kg<br>Methylphenidate dosage: low dose: mean 40 mg (SD 9.2); high dose: mean 76.5 mg (SD 13.2)<br>Administration schedule: once daily, morning, 90 minutes before trial<br>Duration of trial: 3 days<br>Washout before study initiation: 24 hours before participation. No washout between interventions. To promote reasonable tolerability of the medication in participants who were stimulant naive or were previously prescribed only very low doses (0.4 mg/kg/d), 13 children were order-restricted, so they received the 0.3 mg/kg t.i.d.-equivalent dose before receiving the 0.6 mg/kg t.i.d.-equivalent dose. Among those who were not order-restricted, 6 possible drug orders were counterbalanced across participants<br>Treatment compliance: not stated |
| Outcomes | **Non-serious adverse events**<br>1. Adverse events were rated daily by camp counsellors and parents using the Pittsburgh Side Effects Rating Scale<br>2. Blood pressure was rated daily during time of peak medication effects<br>3. Pulse rate was rated daily during time of peak medication effects |

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| **Notes** | Sample calculation: no information<br>Ethics approval: yes<br>**Comment from study authors**<br>1. No child had marked elevation of either cardiovascular parameter<br>**Key conclusion of study authors**<br>1. Findings of the study fit with the clinical literature on ADHD and the hypothesis that methylphenidate enhances interference control for important environmental stimuli<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: no<br>Email correspondence with study authors: wrote to study authors in July 2014 to ask for data on side effects, pulse and blood pressure; have received no response as yet |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No information about randomisation |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Unclear risk | Double-blind, no further information |
| Blinding of outcome assessment (detection bias) | Unclear risk | Double-blind, no further information |
| Incomplete outcome data (attrition bias) | Low risk | No missing data |
| Selective reporting (reporting bias) | Unclear risk | No protocol identified |
| Vested interest bias | Low risk | Supported by grants from the National Institute of Mental Health (NIMH) and from the National Institute on Drug Abuse (NIDA) |

### *Barkley 1989*

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| **Methods** | Triple-blind, randomised, cross-over trial with 3 interventions<br>1. Placebo<br>2. Methylphenidate low dose (0.30 mg/kg)<br>3. Methylphenidate high dose (0.5 mg/kg) |

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| Participants | Number of participants screened: not stated<br>Number of participants included: 83 (71 boys, 12 girls). Participants were randomly assigned to 1 of 6 possible drug condition orders<br>Number of participants followed up: 80<br>Number of withdrawals: 3<br>Diagnosis of ADHD: DSM-III-R (subtype distribution not stated)<br>Age: mean 8.2 years (range 5 to 13)<br>IQ: mean 105.1<br>Methylphenidate naive: 85%<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: mothers, married (n = 48), divorced (n = 13), unmarried or widowed (n = 13)<br>**Inclusion criteria**<br>1. 6 to 13 years of age<br>2. ADHD according to DSM-III-R<br>3. Complaints from teacher, parents or both, of significant inattention, overactivity and impulsivity<br>4. Appearance of symptoms before 7 years of age<br>5. Symptoms for 12 months<br>6. Above the 93rd percentile of the hyperactivity scale on parent or teacher report forms of the Child Behavior Checklist (CBCL)<br>7. Simple language IQ score > 80 on the Peabody Picture Vocabulary Test - Revised<br>**Exclusion criteria**<br>1. Gross sensory or motor deficits<br>2. Tic disorders, Tourette's syndrome or an immediate family history of such<br>3. Seizures<br>4. Gross brain damage<br>5. Autism<br>6. Thought disturbance or schizoid, schizotypal or frank psychotic features<br>7. Significant cardiac problems or high blood pressure<br>8. Excessive levels of anxiety or fear<br>9. Levels of depression that exceed or equal the problems of ADHD<br>10. Most participants (n = 74) were subdivided into children placed 2 SD above the normal mean on the Aggressive scale of the parent form of the Child Behavior Checklist (T score > 70) and those who did not have ≥ 2 SD above the normal mean to form aggressive (n = 37) and non-aggressive subgroups (n = 37). Groups did not differ in age, years of education, maternal age or maternal years of education |

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| Interventions | Participants were randomly assigned to 1 of 6 possible drug condition orders of 0.3 mg/kg methylphenidate, 0.5 mg/kg methylphenidate and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: morning and noon<br>Duration of each medication condition: 7 to 10 days<br>Washout before study initiation: not stated<br>Medication-free period between interventions: not stated<br>Titration period: none<br>Treatment compliance: unused capsules returned to the clinic each week for adherence check<br>No family was discontinued from the study because of non-compliance with the drug regimen, defined as more than 1 day of failure to take medication, or 2 missed capsules per week |
| Outcomes | **ADHD symptoms**<br>1. Conners' Parent Rating Scale - Revised: parent-rated at the end of each drug condition<br>2. Conners' Teacher Rating Scale - Revised: teacher-rated at the end of each drug condition<br>3. Child Attention Profile: teacher-rated at the end of each drug condition<br>**General behaviour**<br>1. Home Situations Questionnaire: parent-rated at the end of each drug condition (7 to 10 days)<br>2. School Situations Questionnaire: teacher-rated at the end of each drug condition (7 to 10 days)<br>**Adverse effects**<br>1. Barkley Side Effects Rating Scale: parent- and teacher-rated at the end of each drug condition (7 to 10 days) |

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| Notes | Sample calculation: not stated<br><br>Ethics approval: Study was approved by the Human Subjects Committee at the medical centre<br><br>**Comments from study authors**<br><br>1. Limitations<br>   a. Rates of side effects were based on a large sample that was screened before admission to the drug trial<br>   b. Low doses of medication to detect side effects<br>   c. Use of rating scale rather than direct behavioural observation<br><br>**Key conclusions of study authors**<br><br>1. In their drug responding, aggressive and non-aggressive participants were quite similar. The few exceptions involved measures of conduct, on which aggressive participants were initially rated as more extreme and subsequently showed a greater degree of improvement from medication than non-aggressive participants<br>2. With this dose range, stimulants result in few/mild side effects; systematic monitoring of side effects suggested before/during clinical trials of stimulants<br><br>**Comment from review authors**<br><br>1. The Barkley Side Effects Rating Scale was labelled generically as a “behaviour questionnaire” to disguise its intended use as a monitoring tool for potential side effects. The purpose was to prevent prejudice on the part of respondents, who might potentially distort their ratings if they knew these could be side effects of the medication<br><br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br><br>Any withdrawals due to adverse events: yes; 3. One child discontinued because of nervous facial tics, headache and dizziness; a second as the result of excessive thinking and disjointed thinking (during high-dose methylphenidate); and a third because of headache, dizziness and increased hyperactivity<br><br>Email correspondence with study authors: July 2013. We obtained additional information regarding funding and ethics approval. Unfortunately, it was not possible to receive from the study authors supplemental data on ADHD symptoms and general behaviour |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | A completely counterbalanced design was used, with participants randomly assigned in relatively equal numbers to 1 of 6 possible drug conditions |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | Both medication and placebo were crushed and placed within orange opaque gelatin capsules to disguise distinctive differences in flavour between medication and placebo and dose differences across conditions. Children and their parents and teachers, as well as the research assistant evaluating the children, were blinded to medication conditions |
| Blinding of outcome assessment (detection bias) | Low risk | Children and their parents and teachers, as well as the research assistant evaluating the children, were blinded to medication conditions |
| Incomplete outcome data (attrition bias) | Unclear risk | No information on incomplete outcome data<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no information |
| Selective reporting (reporting bias) | Low risk | No selective reporting |
| Vested interest bias | Low risk | Study was internally funded by the medical school |

### *Barkley 1991*

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| **Methods** | Triple-blind, placebo-controlled, cross-over design with participants randomly assigned to the following conditions<br>1. Three doses of methylphenidate (5 mg, 10 mg and 15 mg b.i.d.)<br>2. Placebo<br>Each intervention period lasted 1 week |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 40. Participants were randomly assigned to 1 of 6 possible drug condition orders (only 6 drug orders, so the highest dose was never given unless preceded by the moderate dose)<br>Number of participants followed up: 40 (36 boys, 4 girls)<br>Number of withdrawals: 0<br>Diagnosis of ADD: DSM-III-R (+H: 58%, -H: 42%)<br>Age: mean 8.6 years (range 6 to 12)<br>IQ: 103.5<br>Methylphenidate naive: not stated<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: borderline and low internalising symptoms. No others stated<br>Comedication: not stated<br>Sociodemographics: 54.8 on Hollingheads 2 Factor Index<br>**Participants were divided into different categories**<br>1. Based on type of ADD<br>a. ADD with hyperactivity (n = 2)<br>b. ADD without hyperactivity (n = 17)<br>2. Based on severity of internalising symptoms by maternal ratings on the Internalising |

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| | scale of the Child Behavior Checklist (CBCL)<br>a. 'High internalising group' (> 70) (n = 12)<br>b. 'Borderline internalising group' (65 to 70) (n = 17)<br>c. 'Low internalising group' (< 65) (n = 11)<br>**Inclusion criteria**<br>1. Diagnosis of ADD(H) according to DSM-III-R<br>2. IQ estimate of 80 or higher on a standardised IQ test given within the past year or on the Wechsler Intelligence Scale for Children - Revised, given at study screening<br>3. Was the biological child of both current parents or had been adopted by them shortly after birth (within the first year)<br>4. No evidence of deafness, blindness, severe language delay, cerebral palsy, epilepsy, autism or psychosis, as established through medical history, parental interview and child play diagnostic interview<br>Additional criteria for children with combined ADHD<br>1. Teacher complaints of short attention span, impulsivity and overactivity as revealed by parent reports<br>2. Duration of 6 months for these problems<br>3. Age of onset of these problems before 7 years<br>4. Score > 93rd percentile on the Inattention and Overactivity scales of the Child Attention Problems Rating Scale<br>5. No history of treatment with stimulant drugs, or, if such a history, physician consent to stop taking medication for 48 hours before evaluation in the study<br>Additional criteria for children with ADD-H<br>1. Same criteria as for children with combined ADHD, with the exception of the fourth criterion. Instead, score > 93rd percentile on the Inattention scale of the Child Attention Problems Rating Scale, but a score < 84th percentile on the Overactivity scale of the Child Attention Problems Rating Scale<br>Differences regarding the 2 ADHD groups<br>1. They differed significantly on child's IQ score, with the ADD without hyperactivity group scoring significantly lower than the ADD with hyperactivity group. Child IQ was correlated with all of the dependent measures (Measures that we used in this review were not affected by differences in IQ)<br>**Exclusion criteria**<br>1. History of tics or Tourette's syndrome, given the controversy over whether stimulants may create or exacerbate these conditions<br>2. Those with a history of cardiac surgery, high blood pressure or cerebral vascular accident, given the known cardiac pressor effects of stimulants<br>3. Those with a history of adverse reactions to a stimulant |
| Interventions | Participants were randomly assigned to 1 of 6 possible drug condition orders of methylphenidate (5 mg, 10 mg and 15 mg) and placebo<br>Administration schedule: b.i.d., morning and noon<br>Duration of each medication condition: 1 week<br>Washout before study initiation: no<br>Titration period: none, but highest dose was never given unless preceded by moderate dose<br>Compliance: Children were permitted to miss 1 day of medication over 7 days and still remain in the study. No families were removed from this study because of non-compliance as defined in this way |

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| Outcomes | **ADHD symptoms**<br>1. Parent-rated<br>a. Attention Deficit Hyperactivity Disorder Rating Scale: rated at the end of each drug condition order<br>b. Home Situations Questionnaire: number of problem settings and mean severity of problems, rated at the end of each drug condition order<br>2. Teacher-rated (teachers completed questionnaires at the conclusion of each medication condition)<br>a. Self Control Rating Scale<br>b. Child Attention Problems<br>c. School Situations Questionnaire: number of problem settings and mean severity of problems<br>**Non-serious adverse events**<br>1. Home Side Effects Rating Scale: parent-rated at the end of each drug condition order<br>2. School Side Effects Rating Scale: parent-rated at the end of each drug condition order |
| Notes | Sample calculation: no<br>Ethics approval: Study was approved by the Institutional Review Board at the medical centre<br>**Key conclusion of study authors**<br>1. This study indicates that ADHD, inattentive type, and ADHD, combined type, do not show dramatic differences in their manner of responding to methylphenidate across 3 dose levels (5 mg, 10 mg and 15 mg), with both groups displaying generally positive drug responses. However, more children with ADHD, inattentive type, had minimal or no response or did best on the low dose of medication, whereas the vast majority of children with ADHD, combined type, showed a positive response, primarily to moderate to high doses of methylphenidate<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; excluded those with history of adverse reactions, but included both naive and prior users of antipsychotics<br>Email correspondence with study author: 18 January 2013. Dr. Barkley informed us that data from the study on side effects, for example, are no longer available |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomly assigned to 1 of 6 possible drug conditions |
| Allocation concealment (selection bias) | Low risk | Hospital pharmacy prepared placebo (lactose powder) and methylphenidate by crushing and placing them into 6 orange opaque gelatin capsules |
| Blinding of participants and personnel (performance bias) | Low risk | Triple-blind design |
| Blinding of outcome assessment (detection bias) | Low risk | Triple-blind design |
| Incomplete outcome data (attrition bias) | Low risk | No incomplete outcome data<br>Selection bias: no |
| Selective reporting (reporting bias) | Unclear risk | Protocol not available |
| Vested interest bias | Low risk | Research was supported by the National Institute of Mental Health (NIMH)<br>Conflicts of interest: no information |

*Barkley 2000*

| Methods | Double-blind, placebo-controlled, within-participant, cross-over trial with 3 interventions<br>1. Methylphenidate: 5 mg, 10 mg, twice daily<br>2. Amphetamine and dextroamphetamine mixed salts (Adderall): 5 mg, 10 mg, twice daily<br>3. Placebo<br>Phases: 5, but high doses of each stimulant always followed lower dose of the same stimulant |
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| Participants | Number of participants screened: 46<br>Number of participants included: 38. Participants were randomly assigned to 1 of 4 possible drug condition orders<br>Number of participants followed up: 35 (30 boys, 5 girls)<br>Number of withdrawals: 2. One was a post hoc exclusion<br>Diagnosis of ADHD: DSM-IV (subtype not described)<br>Age: mean 14 years (range 12 to 17)<br>IQ: mean 103.9 (range 80 to 141)<br>Methylphenidate naive: not stated<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criterion**<br>1. Adolescents, 12 to 17 years of age, with a DSM-IV diagnosis of ADHD<br>**Exclusion criteria**<br>1. History of motor or vocal tics, Tourette's syndrome, cardiac surgery, high blood pressure, cerebral vascular accident, hyperthyroidism or pregnancy or lactation<br>2. Adverse reactions to stimulant medications |
| Interventions | Participants were randomly assigned to 1 of 4 possible drug condition orders of 5 mg methylphenidate followed by 10 mg methylphenidate, 5 mg Adderall followed by 10 mg Adderall and placebo<br>1. 5 mg, 10 mg methylphenidate; placebo; 5 mg, 10 mg Adderall<br>2. 5 mg, 10 mg Adderall; placebo; 5 mg, 10 mg methylphenidate<br>3. Placebo; 5 mg, 10 mg methylphenidate; 5 mg, 10 mg Adderall<br>4. 5 mg, 10 mg Adderall; 5 mg, 10 mg methylphenidate; placebo<br>Mean methylphenidate dosage: low dose 10 mg/d; high dose 20 mg/d<br>Administration schedule: AM and midday<br>Duration of each medication condition: 1 week<br>Washout before study initiation: none<br>Medication-free period between interventions: none<br>Titration period: none, although 5 mg dose was given before 10 mg, initiated after randomisation<br>Treatment compliance: Parents were required to return all unused capsules, but nothing further was said about this |
| Outcomes | **ADHD symptoms**<br>1. Parent- and teacher-rated ADHD/ODD Rating Scales: completed over previous treatment week<br>**Non-serious adverse events**<br>1. Barkley Side Effects Rating Scale: completed by adolescent, parent and teacher at the end of each treatment week |

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| **Notes** | Sample calculation: not described<br>Ethics approval: yes<br>**Comments from study authors**<br>1. Teens are more independent of their parents than are younger children, spending more time outside parental supervision. This raises serious questions about the sensitivity of parental reports to drug and dose response<br>2. Limitations: Most noteworthy was the poor co-operation of teachers. As a consequence, the statistical power of the study to detect drug effects on these measures, often the most sensitive to stimulant drug effects, was greatly reduced<br>**Key conclusion of study authors**<br>1. In conclusion, the present study suggested that both Adderall and methylphenidate may have been clinically effective in the management of teens with ADHD when non-blinded, global clinical judgements of improvement, which were based on multiple sources of information, were used. Even so, these positive drug responses could not be documented at the group level of statistical analysis by using more specific and systematic ratings by parents and teachers. Clinicians undertaking stimulant trials in such contexts need to be aware of the many challenges to the internal validity of these procedures that are likely to occur in drug trials with teens<br>**Comment from review authors**<br>1. To exclude participants with low IQ was a post hoc decision<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; excluded patients who had a history of adverse events to stimulants<br>Email correspondence with study authors: January 2014. We received additional information |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Email correspondence with study author: “Randomization was done by me as best as I can recall” (Krogh 2014a [pers comm]) |
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Blinding of participants and personnel (performance bias) | Low risk | Opaque gelatin capsules were prepared by the pharmacist |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not stated |
| Incomplete outcome data (attrition bias) | High risk | Completer analysis reported 11/46 teens LTFU, 15 parents LTFU, 33 English teachers and 31 Maths teachers LTFU<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Low risk | Email correspondence with study author: "All planned analyses were done and all measures we collected as treatment endpoints were analyzed" (Krogh 2014a [pers comm]) |
| Vested interest bias | Low risk | University of Massachusetts Medical School |

## *Bedard 2008*

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| **Methods** | Four-day randomised, double-blind, placebo-controlled, cross-over trial with 2 interventions in 2 groups<br>**Interventions**<br>1. Methylphenidate<br>2. Placebo<br>**Groups**<br>1. ADHD with anxiety<br>2. ADHD without anxiety |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 130. Participants were randomly assigned to 1 of 11 possible drug condition orders<br>Number of participants followed up: 130 (110 boys, 20 girls)<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-IV (combined (63%), hyperactive-impulsive (30%), inattentive (6%))<br>Age: mean 9 years (SD 1.46, range 6 to 12)<br>IQ: mean 104.11<br>Methylphenidate naive: 70%<br>Ethnicity: Caucasian (90%)<br>Country: Canada<br>Setting: out-patient clinic<br>Comorbidity: specific learning disorder (34%), conduct disorder (24%), oppositional defiant disorder (26%), generalised anxiety disorder (17%), separation anxiety disorder (11%)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criterion**<br>1. DSM-IV diagnosis via clinical diagnostic assessment: confirmed by Parental Interview for Child Symptoms (PICS) and Teacher Telephone Interview (TTI)<br>**Exclusion criteria**<br>1. IQ < 80<br>2. Evidence of neurological dysfunction, poor physical health or uncorrected sensory impairments<br>3. History of psychosis based on physician enquiry<br>4. Primary language spoken at home not English |
| **Interventions** | Participants were randomly assigned to 1 of 11 possible drug condition orders of methylphenidate and placebo. Children weighing < 25 kg received 5 mg, 10 mg and 15 mg of methylphenidate; children weighing ≥ 25 kg received 10 mg, 15 mg and 20 mg of methylphenidate<br>Mean methylphenidate dosage: 0.28 mg/kg, 0.45 mg/kg, 0.61 mg/kg<br>Administration schedule: not stated<br>Duration of each medication condition: 1 day<br>Washout before study initiation: none<br>Medication-free period between interventions: not stated<br>Titration period: none<br>Treatment compliance: not stated |

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| **Outcomes** | **ADHD symptoms**<br>1. Iowa-Conners' Rating Scale. Scale was completed by the examiner at the end of each session |
| **Notes** | Sample calculation: no<br>Ethics approval: approved by the institutional ethics review board<br>**Comment from study authors**<br>1. We cannot predict that similar results would hold with longer-term treatment or with extended-release preparations<br>**Key conclusions of study authors**<br>1. Findings provide insight into potential mechanisms underlying individual differences in treatment response in ADHD, which may facilitate more targeted treatments<br>2. Results from the present study demonstrate that methylphenidate produces moderate but beneficial effects on selected aspects of working memory that are known to be impaired in ADHD. Furthermore, comorbid anxiety may be a predictor of working memory treatment response<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: December 2013. Not able to get supplemental information from study authors |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Master randomisation tables were prepared by the research support pharmacist at the hospital by using simple randomisation with restrictions (high dose not to be given on the first possible drug day nor immediately following placebo; no directly ascending or descending dose order). Therefore, a balanced block 22 design was used |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | Examiner, psychiatrist, participant and participant's family were not informed about participant's randomisation order or daily medication status until completion. Placebo and active medication were prepared by the hospital pharmacist and were powdered and packaged in an opaque capsule to prevent identification of contents by colour, taste or volume |
| Blinding of outcome assessment (detection bias) | Low risk | Trained clinicians, blinded to other aspects of the participant's assessment, conducted interviews independently |
| Incomplete outcome data (attrition bias) | Low risk | No drop-outs<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | No protocol available |
| Vested interest bias | Low risk | Funding and operating grant from the Canadian Institute of Health Research and funding from the Canada Research Chairs Programme<br>Conflicts of interest: none |

***Ben 2002***

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| **Methods** | Two-week, double-blind, placebo-controlled, cross-over trial with 1 intervention<br>1. Methylphenidate 0.5 mg/kg/d<br>2. Placebo<br>The purpose of the study was to investigate the relationship between SLC6A3 3' end variable number tandem repeat (VNTR) polymorphism and behavioural/therapeutic response to methylphenidate<br>Phases: not stated |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 42 (all boys). Participants were randomly assigned to 1 of 2 possible drug condition orders<br>Number of participants followed up: not stated<br>Number of withdrawals: not stated<br>Diagnosis of ADHD: DSM-IV (subtype not stated)<br>Age: mean 9.2 ± 1.8 years (range not stated)<br>IQ: not stated<br>Methylphenidate naive: not stated<br>Ethnicity: not stated<br>Country: Canada<br>Setting: not stated<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criterion**<br>1. Not stated<br>**Exclusion criterion**<br>1. Not stated |
| **Interventions** | Participants were randomly assigned to 1 of 2 possible drug condition orders of methylphenidate (0.5 mg/kg/d) and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: not stated<br>Time points: not stated<br>Duration of each medication condition: not stated<br>Washout before study initiation: not stated<br>Medication-free period between interventions: not stated<br>Titration period: not stated. No information<br>Treatment compliance: not stated |
| **Outcomes** | **General behaviour**<br>1. Conners' Continuous Performance Test Overall Index: before and 45 minutes after administration of placebo or methylphenidate<br>2. Restricted Academic Situation Scale: before and 45 minutes after administration of placebo or methylphenidate<br>3. Conners' Global Index Scale: parent and teacher reports, time points not stated |

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| **Notes** | Sample calculation: not stated<br>Ethics approval: not stated<br>**Key conclusion of study authors**<br>1. Although preliminary, these results suggest that the SLC6A3 3' end variable number tandem repeat may modulate therapeutic response to methylphenidate as evaluated by teachers<br>**Comments from review authors**<br>1. Abstract only. Abstract includes no raw information on clinical effectiveness; includes mostly details of the relationship gene/methylphenidate effect<br>2. No information on adverse events was provided in this abstract<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: not stated<br>Any withdrawals due to adverse events: not stated<br>Email correspondence with study authors: October 2013 and April 2014. We wrote to the study authors twice to request supplementary information on data. No reply was received. Therefore we have no useable data from this study |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not stated |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Unclear risk | Not stated |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not stated |
| Incomplete outcome data (attrition bias) | Unclear risk | Inadequate information contained in the abstract<br>Selection bias: not stated |
| Selective reporting (reporting bias) | Unclear risk | Protocol not available |
| Vested interest bias | Unclear risk | Not stated |

### *Biederman 2003*

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| **Methods** | Fifteen-site, multi-centre, double-blind, randomised, 2-week parallel trial with 2 arms<br>1. Extended-release methylphenidate (Ritalin LA)<br>2. Placebo<br>Phases: 3. Pre-randomisation (4 weeks titration plus 1 week washout), randomisation, double-blind treatment and open-label extension |

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| Participants | Number of participants screened: unknown<br>Number of participants included: 164<br>Number of participants titrated: 161 (122 boys, 39 girls)<br>Number of participants randomly assigned: methylphenidate 66, placebo 71<br>Number of participants followed up: methylphenidate 63, placebo 71<br>Number of withdrawals: methylphenidate 3, placebo 0<br>Diagnosis of ADHD: DSM-IV (combined (75.8%), hyperactive-impulsive (1.2%), inattentive (18.6 %))<br>Age: mean 8.81 years (range 6 to 14)<br>IQ: not stated<br>Methylphenidate naive: 94 (58.4%)<br>Ethnicity: Caucasian (85.7%), African American (3.7%), Asian (1.2%), other (9.3%)<br>Country: USA and Canada<br>Setting: out-patient clinic (naturalistic school setting)<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated. No significant difference in baseline demographics were noted between the 2 groups<br>**Inclusion criteria**<br>1. Boys and girls 6 to 14 years of age who met DSM-IV criteria for ADHD and were receiving treatment with methylphenidate, or de novo patients<br>2. Meeting ADHD criteria in the structured diagnostic interview (National Institute of Mental Health Diagnostic Interview Schedule for Children, Fourth Edition)<br>3. Attending school in a classroom setting with the same teacher, who, for the duration of the study, would perform weekly assessments<br>4. Functioning, in the opinion of the investigator, at age-appropriate levels academically<br>5. Female patients of childbearing age needed to have a negative pregnancy test and if sexually active had to be using adequate and reliable contraception for the duration of the study<br>6. Ongoing behavioural therapies for ADHD were permitted to continue, but participants were not to initiate behavioural therapy during the trial<br>7. Informed consent<br>**Exclusion criteria**<br>1. Patients with somatic or psychiatric disorders that could contraindicate treatment or confound efficacy or safety assessments, or those who required treatment with drugs other than methylphenidate<br>2. Known hypersensitivity to the study drug<br>3. Likelihood of non-compliance<br>4. History of substance abuse<br>5. Living with a person with a substance abuse disorder<br>6. Pregnancy<br>7. Use of other investigational drugs during the study period |
| Interventions | Participants were randomly assigned to extended-release methylphenidate or placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: once daily in the morning<br>Duration of intervention: 2 weeks (mean: methylphenidate 13.91, placebo 13.96)<br>Titration period: 1 week before randomisation<br>Treatment compliance: 130 completed treatment (methylphenidate 61, placebo 69) |

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| Outcomes | **ADHD symptoms**<br>1. Primary efficacy outcome measure<br>a. Conners' ADHD/DSM-IV Scale, Teachers: Total subscale, school day weekly assessments<br>2. Secondary efficacy measure<br>a. Conners' ADHD/DSM-IV Scale, Teachers: Inattentive subscale<br>b. Conners' ADHD/DSM-IV Scale, Teachers: Hyperactive-Impulsive subscale<br>c. Conners' ADHD/DSM-IV Scale, Parents: Total subscale, weekends<br>d. Conners' ADHD/DSM-IV Scale, Parents: Inattentive subscale<br>e. Conners' ADHD/DSM-IV Scale, Parents: Hyperactive-Impulsive subscale<br>**Non-serious adverse events**<br>1. Monitoring of adverse events<br>2. Routine laboratory tests (haematology, blood chemistry, urine)<br>3. Vital signs (sitting blood pressure and pulse)<br>4. Height, weight and performance of physical examinations and drug screening |
| Notes | Sample calculation: yes. A total of 128 participants (n = 64 per treatment group) were required for analysis of the primary efficacy variable, based on an effect size of 0.5 with a power of 80% and a 2-tailed α-level of 0.05<br>Ethics approval: yes. An institutional review board approved this study at each participating site<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes<br>Any withdrawals due to adverse events: yes<br>**Comment from study authors**<br>1. Limitations: First, participants in this study were primarily male Caucasians with ADHD. Second, the short study duration does not predict long-term efficacy or safety. Third, selection of responders during the titration phase may have affected the outcomes of this study. In clinical practice, response rate may be lower than that observed among the current sample<br>**Key conclusion of study authors**<br>1. Results demonstrate that extended-release methylphenidate (Ritalin LA) administered once daily for up to 2 weeks achieved outcomes statistically superior to placebo in children with ADHD<br>**Comments from review authors**<br>1. Mean methylphenidate dosage not stated, only range (10 mg/d to 40 mg/d)<br>2. IQ not stated<br>Email correspondence with study authors. April 2014. Emailed study authors for additional information/data but have not received a response |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomisation was performed by Novartis Drug Supply Management, which used a validated system that automates random assignment of treatment groups to randomisation numbers |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Unclear risk | Not clear whether investigator was blinded |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not clear whether investigator was blinded |
| Incomplete outcome data (attrition bias) | Low risk | LOCF analysis of ITT population. ITT population included all participants who received the double-blind study drug, and from whom ≥ 1 Conners' ADHD/DSM-IV Scale, Teachers, was obtained |
| Selective reporting (reporting bias) | Low risk | No protocol was published. Outcomes of interest have been reported |
| Vested interest bias | High risk | Funding was received from Novartis |

*Bliznakova 2007*

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| **Methods** | Eleven-day N-of-1 randomised, double-blind, cross-over trial with 2 interventions<br>1. Methylphenidate<br>2. Placebo |
| **Participants** | Number of participants screened: 1 boy<br>Number included: 1. The participant was randomly assigned to methylphenidate and placebo across the 11 days<br>Number of participants followed up: 1<br>Number of withdrawals: 1<br>Diagnosis of ADHD: ICD-10 (predominantly hyperactive type)<br>Age: 15 years<br>IQ: not stated<br>Methylphenidate naive: no<br>Ethnicity: not stated<br>Country: Germany<br>Setting: not stated<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: 2 parents |
| **Interventions** | The participant was randomly assigned to methylphenidate and placebo across 11 days<br>Mean methylphenidate dosage: not stated<br>Administration schedule: not stated<br>Duration of each medication condition: The condition was changed daily, but placebo was given for 6 days and methylphenidate for 5 days<br>Washout before study initiation: not relevant<br>Medication-free period between interventions: no<br>Titration period: none<br>Treatment compliance: 100% according to Table 6 |
| **Outcomes** | **ADHD symptoms**<br>1. Conners' Teacher Rating Scale: rated daily<br>2. Parent/Teacher Rating Scale: rated daily<br>**Non-serious adverse events**<br>1. Assessment of stomachaches (yes/no) daily |
| **Notes** | Sample calculation: yes<br>Ethics approval: not stated<br>**Key conclusion of study authors**<br>1. Double-blind study showed significant symptom reduction under the medication condition, which was also noted by the participant himself. Furthermore, towards the end of the study, the somatic complaints were gone<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: no<br>Email correspondence with study authors: December 2013. Emailed study author to request information about missing data but received no response. Not possible to use data from this study |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not stated |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Unclear risk | Double-blind |
| Blinding of outcome assessment (detection bias) | Unclear risk | Double-blind |
| Incomplete outcome data (attrition bias) | Low risk | No<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Low risk | No |
| Vested interest bias | Unclear risk | Not stated<br>Conflicts of interest: not stated |

*Blum 2011*

| Methods | This double-blind, placebo-controlled, cross-over trial with the child's clinically most effective dose as identified by a systematic open-label titration procedure investigated whether components of attention and executive functioning improve when children with ADHD are treated with OROS methylphenidate<br>Two-week, cross-over trial with 2 interventions<br>1. OROS methylphenidate<br>2. Placebo |
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| Participants | Number of participants screened: 41<br>Number of participants included: 34. Participants were assigned to OROS methylphenidate and placebo in random order<br>Number of participants followed up: 30 (24 boys, 6 girls)<br>Number of withdrawals: 4<br>Diagnosis of ADHD: DSM-IV TR (combined (100%))<br>Age: mean 8 years 6 months (range 6 years 5 months to 12 years 6 months)<br>IQ: mean 97.8 (range 77 to 132)<br>Methylphenidate naive: number not stated<br>Ethnicity: Caucasian (80%), African American (13.3%), other (6.7%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity type: oppositional defiant disorder (40%), specific learning difficulty (33.3%), anxiety (6.67%), dysthymia (3.3%)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Children 6 to 12 years of age, in first grade or higher<br>2. DSM-IV-TR diagnosis of ADHD combined type<br>3. Parent and teacher ratings on the ADHD Rating Scale, Fourth Edition, of at least the 85th centile for hyperactivity/impulsivity and inattention, or both (if the child was not taking medication at enrolment)<br>4. IQ > 75 on the Wechsler Abbreviated Scale of Intelligence<br>**Exclusion criteria**<br>1. Children with a past or current diagnosis of a chronic tic disorder, a pervasive developmental disorder, cerebral palsy, bipolar disorder, major depression, head injury requiring hospitalisation, psychotic disorder, glaucoma, cardiovascular disease, epilepsy, obsessive-compulsive disorder serious enough to warrant separate treatment or suicidal or homicidal behaviour or ideation<br>2. History of side effects with methylphenidate requiring discontinuation of the medication<br>3. Children were also excluded if they were known to be unable to swallow a tablet<br>4. Use within 14 days of a monoamine oxidase inhibitor<br>5. Long-term treatment with coumarin, clonidine or tricyclic antidepressants |
| Interventions | Participants were randomly assigned to OROS methylphenidate and placebo<br>Methylphenidate dosage: 9 children treated with 18 mg, 13 with 36 mg and eight with 54 mg of OROS methylphenidate<br>Administration schedule: not stated<br>Duration of each medication condition: 1 week<br>Washout before study initiation: not stated<br>Medication-free period between interventions: not stated<br>Titration period: 2- to 3-week open-label, multi-dose-titration protocol to determine the child's optimal dose as recommended by practice guidelines<br>Treatment compliance: 30 children completed the study; however, compliance regarding study medication is not stated |

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| Outcomes | **ADHD symptoms**<br>1. ADHD Rating Scale, Fourth Edition, both parent- and teacher-rated: rated at the end of each week of the different medication trial<br>**Non-serious adverse events**<br>1. Stimulant Drug Side Effects Rating Scale, parent-rated: rated at the end of each week of the different medication trial. These data are not reported in the article |
| Notes | Sample calculation: not stated<br>Ethics approval: yes; approved by the Committee for the Protection of Human Subjects at The Children's Hospital of Philadelphia<br>**Comment from study authors**<br>1. In conducting analyses for the cross-over study, our team examined the effects of crossing participants from the first treatment condition to the second treatment condition (i.e. the carry-over effect).(.....) Because no statistically significant sequence effects were noted, data from both periods were combined, and final analyses were reduced to paired comparisons<br>**Key conclusion of study authors**<br>1. When OROS methylphenidate was used to treat children with ADHD at the clinically most effective dose, general improvement was noted on tasks requiring response inhibition; response to treatment in other domains was variable or was not demonstrated<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes<br>Email correspondence with study authors: January 2014: Emailed study authors twice to request additional information but received no response |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomly assigned and counterbalanced across participants |
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Blinding of participants and personnel (performance bias) | Unclear risk | Referred to as double-blind but no information provided |
| Blinding of outcome assessment (detection bias) | Unclear risk | Referred to as double-blind but no information provided |
| Incomplete outcome data (attrition bias) | High risk | Completer analysis reported |
| Selective reporting (reporting bias) | Low risk | Clinical trial ID: NCT00530257 |
| Vested interest bias | High risk | Study was supported by an investigator-initiated grant from Ortho McNeil Janssen Scientific Affairs, the manufacturer of OROS methylphenidate (Concerta) |

## *Borcherding 1990*

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| Methods | Eleven-week, double-blind, placebo-controlled, cross-over study with 3 interventions<br>1. Methylphenidate<br>2. Dextroamphetamine<br>3. Placebo |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 46 (all boys). Participants were randomly assigned to 1 of the possible drug condition orders<br>Number of participants followed up: 45<br>Number of withdrawals: 1<br>Diagnosis of ADHD: DSM-III (subtype not stated)<br>Age: mean 8.6 years (range 6 to 12)<br>IQ: mean 106.1 (range > 80)<br>Methylphenidate naive: 13 have not received past stimulant treatment<br>Ethnicity: Caucasian (72%), African American (22%), Asian/Hispanic (6%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: medically healthy<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Medically healthy<br>2. Full-scale IQ score > 80 on the Wechsler Intelligence Scale<br>3. Score 2 SD or above age norms on Factor 4 (Hyperactivity) of Conners' Teacher Rating Scale<br>**Exclusion criteria**<br>1. Medical or neurological disease, including chronic motor tics or Tourette's syndrome<br>2. Other primary Axis I psychiatric disorders |
| Interventions | Participants were randomly assigned to 1 of the possible drug condition orders of methylphenidate, dextroamphetamine and placebo<br>Mean methylphenidate dosage: 1.3 mg/kg<br>Administration schedule: twice daily, 9:00 AM and 1:00 PM<br>Duration of each medication condition: 3 weeks<br>Washout before study initiation: 2 weeks<br>Medication-free period between interventions: none<br>Titration period: During the 3 weeks, low dose was given week 1, intermediate dose week 2 and high dose week 3<br>Treatment compliance: not stated |
| Outcomes | **Non-serious adverse events**<br>1. Subject Treatment Emergent Symptom Scale completed weekly by the physician and the child's parents; reflected both symptoms and observed effects<br>2. Attention given to onset and duration of abnormal movements or obsessive-compulsive behaviours. Collected from several sources |

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| **Notes** | Sample calculation: no<br>Ethics approval: not stated<br>**Comment from study authors**<br>1. Most movements and compulsive behaviours were seen only by staff sensitive to these possible effects<br>**Key conclusions of study authors**<br>1. Dextroamphetamine tended to produce more compulsive behaviours, which were also more likely to resemble obsessive-compulsive disorder, than did methylphenidate<br>2. Abnormal movements and compulsive behaviours tended to co-occur with methylphenidate only; no general Tourette's-obsessive-compulsive disorder diathesis was found for this population<br>3. An important clinical point from these data is that abnormal movements and compulsive behaviour due to treatment with 1 stimulant should not necessarily be a cause for discontinuation of stimulant drug treatment; rather, the same stimulant at a different dose or a different stimulant should be tried<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Double-blind random fashion |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | Oral medication in identical capsules was administered at 9:00 AM and 1:00 PM |
| Blinding of outcome assessment (detection bias) | Unclear risk | Double-blind |
| Incomplete outcome data (attrition bias) | Low risk | All participants except 1 (who experienced adverse events) completed the study<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Unclear risk | No protocol; however, all outcomes stated in the Methods have been reported |
| Vested interest bias | Unclear risk | Not stated<br>Conflicts of interest: not stated |

### *Brams 2008*

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| **Methods** | Randomised, double-blind, cross-over, multi-centre study evaluating the efficacy of the following over an 8-hour laboratory classroom day in children with ADHD<br>1. Extended-release dexmethylphenidate (20 mg/d)<br>2. Placebo<br>**Phases**<br>1. Baseline: day 0<br>2. Period 1: days 1 to 7 (Sunday to Saturday), when Saturday is assessment day (8-hour laboratory classroom day)<br>3. Period 2: days 7 to 15<br>4. Final visit: day 15 |

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| Participants | Number of participants screened: 92<br>Number of participants included: 86 (53 boys, 33 girls). Participants were randomly assigned to 1 of 2 possible drug condition orders<br>Number of participants followed up: 86<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-IV (combined (87.2%), hyperactive-impulsive (0%), inattentive (12.8%))<br>Age: mean 9.5 years (range 6 to 12)<br>IQ: > 70<br>Methylphenidate naive: 0%<br>Ethnicity: Caucasian (48.8%), African American (24.4%), Asian (2.3%), Hispanic (23.3%)<br>Country: USA<br>Setting: multi-centre, out-patient clinic<br>Comorbidity: not stated<br>Comedication: no antidepressant or other antipsychotic medication<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. DSM-IV criteria for a diagnosis of ADHD of any type, as established by the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Versions<br>2. 6 to 12 years of age<br>3. Only children whose parents or legal guardians, or both, provided written informed consent before any study-related procedures were performed were enrolled<br>4. Females of child-bearing potential were required to have a negative urine pregnancy test before enrolment and, if sexually active, to be using adequate and reliable contraception (e.g. double-barrier method), which was documented in the medical record<br>**Exclusion criteria**<br>1. Children or their parents/guardians were unable to understand or follow instructions as needed to participate in the study<br>2. Children deemed by investigators to have below-average cognitive capacity, or to be home-schooled<br>3. Previously diagnosed with Gilles de la Tourette's syndrome or a tic disorder (medication-induced tics were not excluded)<br>4. History of seizure disorder, or history of, or concurrent, significant medical or psychiatric illness or substance abuse disorder<br>5. Taking an antidepressant or other antipsychotic medication; those who initiated psychotherapy within the 3 months preceding screening and those with a positive urine drug screen were deemed ineligible<br>6. Poor response or known sensitivity to all methylphenidate or dexmethylphenidate formulations based on past medical history<br>7. Taking other medications for ADHD<br>8. Prospective participants taking or planning to take any other investigational drug within 30 days of the start of the study<br>9. Previously participated in an analogue classroom study within 6 months before screening. |

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| Interventions | Participants were randomly assigned to 1 of 2 possible drug condition orders of once-daily, extended-release dexmethylphenidate 20 mg (Focalin XR (Novartis Pharmaceuticals Corporation) and placebo<br><br>Mean methylphenidate dosage: 20 mg<br><br>Administration schedule: once daily in the morning<br><br>Duration of each medication condition: 7 days<br><br>Washout before study initiation: 1 week before the study<br><br>Titration period: Before study participation, all participants were stabilised on a total daily dose or nearest equivalent dose of methylphenidate 40 mg to 60 mg or dexmethylphenidate 20 mg to 30 mg for ≥ 2 weeks before screening<br><br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br><br>1. Primary efficacy outcome<br>a. Change on the Swanson, Kotkit, Agler, M-Flynn and Pelham Scale: combined score from pre-dose to the 0.5-hour post-dose time point during the 8-hour classroom day. Rated by observer<br>b. Change in Swanson, Kotkit, Agler, M-Flynn and Pelham Scale: combined scores from pre-dose to 1, 2, 4, 6 and 8 hours post dose. Rated on classroom day by observers<br>c. Change from pre-dose on Swanson, Kotkit, Agler, M-Flynn and Pelham Scale: Attention and Deportment scores at all time points (0.5, 1, 2, 4, 6 and 8 hours post dose)<br>d. Conners' ADHD/DSM-IV Scales, Parent: completed by parent/legal guardian on classroom day<br><br>**Non-serious adverse events**<br><br>1. Vital signs: recorded at each visit (days 0, 7, 14)<br>2. Spontaneously reported adverse events, including serious adverse events, at the end of each treatment period<br>3. Heart rate and blood pressure measured at pre-dose, 4 and 8 hours post dose at days 7 and 14<br>4. Weight at screening and at day 15<br>5. ECG at screening and at day 15 |

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| **Notes** | Sample calculation: yes<br><br>Ethics approval: not stated<br><br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; children with poor response or known sensitivity to methylphenidate or dexmethylphenidate were excluded<br><br>**Comments from study authors**<br><br>1. Several limitations with regard to the design of this study should be considered in interpretation of these data<br>2. Participant population was required to have had previous exposure to methylphenidate or dexmethylphenidate. It is likely that this patient population already demonstrated a therapeutic response to methylphenidate or dexmethylphenidate, as well as tolerance to these drugs<br>3. Only a fixed dosage of 20 mg/d was evaluated, making it difficult to compare results observed in the current study with those of other doses currently available, or when treatment is optimised<br><br>**Key conclusions of study authors**<br><br>1. Compared with placebo, once-daily, extended-release dexmethylphenidate 20 mg provided rapid and significant improvement at 0.5 hours post dose in attention, deportment and academic performance, which was sustained for 8 hours post dose<br>2. Overall, once-daily extended-release dexmethylphenidate 20 mg was well tolerated<br>3. In an analysis of parental assessment of diary responses, children appeared better organised, and morning preparation for school was smoother and less frustrating, with once-daily extended-release dexmethylphenidate compared with placebo<br><br>Email correspondence with study authors: September 2013. We received an email from Dr. Brams, in which we were told that Novartis had control and ownership of study data. Consequently, we had to contact the Public Affairs Department at Novartis to request the information (e.g. protocols) (Krogh 2013a [pers comm]) |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The randomisation list was generated by the study sponsor, who used an automated random assignment of treatment sequences to randomisation numbers in the specified ratio |
| Allocation concealment (selection bias) | Low risk | All study medications and packaging were identical in appearance for blinding purposes |
| Blinding of participants and personnel (performance bias) | Low risk | Participants, parents, study centre personnel and those who assessed outcomes were blinded to study treatment |
| Blinding of outcome assessment (detection bias) | Low risk | Participants, parents, study centre personnel and those who assessed outcomes were blinded to study treatment |
| Incomplete outcome data (attrition bias) | Low risk | The safety population consisted of all participants who took ≥ 1 dose of study medication. The efficacy population included all randomly assigned participants who provided valid efficacy measurements for both treatment periods<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | Not stated |
| Vested interest bias | High risk | Sponsored by Novartis Pharmaceuticals Corporation<br>Conflicts of interest: First study author has been a speaker, consultant and advisory board member for Novartis and Shire |

*Brams 2012*

| Methods | Randomised, double-blind, 3-period × 3-treatment cross-over study in a 12-hour laboratory classroom setting with 3 interventions<br>1. 20 mg extended-release dexmethylphenidate<br>2. 30 mg extended-release dexmethylphenidate<br>3. Placebo<br>Each period lasted 7 days |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 165. Participants were randomly assigned to 1 of 6 possible drug condition orders<br>Number of participants followed up: 157<br>Number of withdrawals: 8<br>Diagnosis of ADHD: DSM-IV (combined or predominantly hyperactive-impulsive subtype)<br>Age: mean 9.6 years (range 9.3 to 10.0)<br>IQ: above normal<br>Sex: 57% boys, 43% girls<br>Methylphenidate naive: 0%<br>Ethnicity: Caucasian (38.2%), African American (31.5%), Hispanic (22.4%), other (7.9%)<br>Country: USA<br>Setting: out-patient clinic (laboratory classroom)<br>Comorbidity: no significant medical illness<br>Comedication: no information<br>Sociodemographics: no information<br>**Inclusion criteria**<br>1. Males and females 6 to 12 years of age<br>2. Meeting DSM-IV criteria for primary diagnosis of ADHD combined subtype or predominantly hyperactive-impulsive subtype<br>3. Female of childbearing potential required to have a negative urine pregnancy test before enrolment and, if sexually active, to use adequate and reliable contraception<br>4. Stabilised on a total daily dose or nearest equivalent dose of 40 mg to 60 mg of methylphenidate or 20 mg to 30 mg dexmethylphenidate (36 mg and 54 mg of extended-release methylphenidate and 10 mg to 20 mg of transdermal methylphenidate were allowed) for ≥ 2 weeks before screening<br>**Exclusion criteria**<br>1. Children or their parents/guardians were unable to understand or follow instructions necessary to responsibly participate in the study<br>2. Children were deemed by the investigator to have below average cognitive ability<br>3. Home-schooled<br>4. Previously diagnosed with Gilles de la Tourette's disorder or similar tic disorder (medication-induced tics were not excluded)<br>5. History of a seizure disorder<br>6. History of or concurrent long QT syndrome or QTc > 450 milliseconds at screening, or any clinically significant ECG abnormality<br>7. Significant medical or psychiatric illness or substance abuse disorder<br>8. Children were taking an antidepressant or other antipsychotic medications<br>9. Children initiated psychotherapy within the 3 months before screening<br>10. Positive urine drug screen<br>11. Children with a poor prior response, or known sensitivity, to all methylphenidate or D-MPH products, based on medical history<br>12. Children currently taking non-methylphenidate-based medications for ADHD<br>13. Those taking or planning to take any other investigational drug within 30 days of study start<br>14. Children who had previously participated in an analogue classroom study within 6 months before screening<br>15. Alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase or serum creatinine > 2× the upper limit of normal at screening |

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| Interventions | Participants were randomly assigned to 1 of 6 possible drug condition orders of 20 mg extended-release dexmethylphenidate, 30 mg extended-release dexmethylphenidate and placebo<br>Administration schedule: once daily, morning<br>Duration of each medication condition: 7 days<br>Washout before study initiation: 1 week<br>Medication-free period between interventions: no<br>Titration period: none (fixed doses)<br>Treatment compliance: no information |
| Outcomes | **ADHD symptoms**<br>1. Swanson, Kotkit, Agler, M-Flynn and Pelham Scale (-combined, -attention and -deportment): performed by independent blinded raters throughout the 12-hour testing period<br>**Serious adverse events**<br>1. Spontaneously reported serious adverse events were recorded weekly<br>One participant experienced 2 serious adverse events (peritonsillar abscess and oral bullae) while receiving 20 mg extended-release dexmethylphenidate and was hospitalised for 6 days for the peritonsillar abscess. Serious adverse events were considered not related to study drug. Participant discontinued the study for missed study drug during hospitalisation<br>**Non-serious adverse events**<br>1. Vital signs were assessed, and spontaneously reported adverse effects were recorded weekly<br>2. Heart rate and blood pressure were measured after weeks 1 and 2<br>3. Weight was measured and ECG tests were conducted at screening and at the final visit |

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| Notes | Sample calculation: no<br><br>Ethics approval: yes<br><br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; children with a poor prior response, or known sensitivity, to all methylphenidate or dexmethylphenidate products based on medical history were excluded<br><br>**Comments from study authors (limitations)**<br><br>1. Limited exposure to both doses of extended-release dexmethylphenidate for each participant to 1 week<br>2. Potential for carry-over effects between study periods due to cross-over design<br>3. Children with the inattentive subtype of ADHD were excluded from this analysis<br>4. Efficacy data presented as change from pre-dose scores, rather than as effect sizes or response rates<br>5. Pharmacokinetic and pharmacodynamic data were not collected and analysed<br>6. Results reported for school-aged children may not be relevant to other ADHD patient populations<br>7. Higher percentage of females recruited<br><br>**Key conclusions of study authors**<br><br>1. Significantly greater improvement in ADHD symptoms was noted with 30 mg extended-release dexmethylphenidate compared with 20 mg extended-release dexmethylphenidate at hours 10 through 12<br>2. Tolerability was comparable between doses. 30-mg dose of extended-release dexmethylphenidate may provide further benefit to patients who do not maintain optimal symptom control later in the day with 20-mg extended-release dexmethylphenidate<br>3. ADHD symptoms significantly improved with 30 mg extended-release dexmethylphenidate compared with 20 mg extended-release dexmethylphenidate at hours 10 to 12 in all ethnic parameters, with a statistically significant difference in the Caucasian subgroup<br>4. 30 mg extended-release dexmethylphenidate may provide further benefit to patients of all ethnic backgrounds who do not obtain optimal late-day symptom control with 20 mg extended-release dexmethylphenidate<br><br>Email correspondence with study authors: September 2013. Not possible to contact study authors |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Participants were randomly assigned to 1 of 6 treatment sequences. All participants were given the lowest available number from the randomisation numbers provided at each site. A randomisation list was produced by using a validated system that automated the random assignment of treatment sequences to randomisation numbers in the specified ratio |
| Allocation concealment (selection bias) | Low risk | Randomisation data were kept strictly confidential until the time of unblinding |
| Blinding of participants and personnel (performance bias) | Low risk | All study medications and packaging were identical in appearance for blinding purposes. Participants, parents, study centre personnel and those who assessed outcomes were blinded to study treatment |
| Blinding of outcome assessment (detection bias) | Low risk | All study medications and packaging were identical in appearance for blinding purposes. Participants, parents, study centre personnel and those who assessed outcomes were blinded to study treatment |
| Incomplete outcome data (attrition bias) | Low risk | Eight drop-outs from the methylphenidate group. The ITT population included all randomly assigned participants who took ≥ 1 dose of study medication and had ≥ 1 post-dose efficacy measurement. The safety population consisted of all participants who took ≥ 1 dose of study medication<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | No information |
| Vested interest bias | High risk | Funding by Novartis Pharmaceuticals Corporation with the following involvement reported: design and conduct of the study; collection, management, analysis and interpretation of data; and preparation, review and approval of the manuscript. All study authors are employees or consultants or have received research grants from pharmaceutical companies<br>Conflicts of interest: All study authors are employees or consultants or have received research grants from pharmaceutical companies |

### *Brown 1984a*

| Methods | Four-week cross-over trial with 2 interventions<br>1. Methylphenidate<br>2. Placebo<br>Phases: 2 weeks of placebo and 2 weeks of methylphenidate treatment with sequence according to randomisation |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 11 (all boys). Participants were randomly assigned to 1 of 2 possible drug condition orders<br>Number of participants followed up: 11<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-III<br>Age: mean 10 years, 5 months (range 9 years 1 month to 12 years 1 month)<br>IQ: > 80<br>Methylphenidate naive: not stated<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criterion**<br>1. DSM-III diagnosis of ADD<br>**Exclusion criteria**<br>1. Known neurological or sensory impairment<br>2. IQ > 80 |
| Interventions | Participants were randomly assigned to 1 of 2 possible drug condition orders of 0.3 mg/kg methylphenidate and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: b.i.d.<br>Duration of each medication condition: 2 weeks<br>Washout before study initiation: not stated<br>Medication-free period between interventions: time of day the pills were taken not stated<br>Titration period: none<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. Conners' Parent Rating Scale: rated at the end of each school week<br>2. Conners' Teacher Rating Scale: rated at the end of each school week<br>**Non-serious adverse events**<br>1. Cardiovascular measures: heart rate, systolic and diastolic blood pressure. Heart rate was recorded after the child had rested for 5 minutes by placing a stethoscope over the precordium and measuring the rate for 1 minute. Blood pressure was obtained with a sphygmomanometer with the child seated after he had rested 5 minutes. Tested at the end of each 2-week drug period<br>2. “No deleterious side effects” |

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| **Notes** | Sample calculation: no<br>Ethics approval: yes<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Comments from study authors**<br>1. Of additional importance in the present study was the finding that methylphenidate had no deleterious side effects and was well tolerated by all children participating in the research project<br>2. Table 2 shows that individual variations in heart rate and blood pressure associated with methylphenidate trials are quite large<br>**Key conclusions of study authors**<br>1. Results demonstrated significant improvement in sustained attention and impulse control, as well as in ratings of social behaviour, by both teachers and parents<br>2. Cardiovascular functioning did not significantly increase as a function of methylphenidate<br>Email correspondence with study authors: November 2013. We received additional information regarding ethics approval, sample calculation, etc., from study authors. However, it was not possible to receive all requested data, as the study author no longer possessed raw data from the study |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | The sequence of the 2 medication conditions was randomly assigned, but no information was provided on methods |
| Allocation concealment (selection bias) | Low risk | Triple blinding; dosage was administered twice daily in the form of opaque capsules packaged by hospital pharmacists to conceal the contents |
| Blinding of participants and personnel (performance bias) | Low risk | Child and parent, teacher and the physician were blinded to the child's medication condition |
| Blinding of outcome assessment (detection bias) | Low risk | Physician was blinded to the child's medication concealment |
| Incomplete outcome data (attrition bias) | Low risk | Data provided on all 11 participants<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Low risk | No |
| Vested interest bias | Unclear risk | Funded by National institute of Mental Health and National institutes of Health. Placebo and methylphenidate were supplied by CIBA-GEIGY Corporation, Summit, New Jersey<br>Conflicts of interest: not stated |

### *Brown 1985*

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| **Methods** | Twelve-week, randomised, parallel trial with 4 arms<br>1. Cognitive training<br>2. Methylphenidate combined with cognitive training<br>3. No treatment (not randomly assigned)<br>4. Cognitive training programme: individual, twice-weekly, 1-hour sessions for a total of 24 sessions spanning a 3-month period |

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| Participants | Number of participants included: methylphenidate + cognitive training 10, cognitive training 10<br>Number of participants followed up: methylphenidate + cognitive training 10, cognitive training 10<br>Number of withdrawals: methylphenidate + cognitive training 0, cognitive training 0<br>Diagnosis of ADHD: DSM-III (types not stated)<br>Age: mean 11.36 years (range 6.4 to 11.9)<br>IQ: 101.92 (range 91 to 136)<br>Methylphenidate naive: not stated<br>Ethnicity: not stated<br>Country: USA<br>Setting: not stated<br>Comorbidity: not stated<br>Comedication: no. No child was receiving any psychopharmacological treatment<br>Sociodemographics: not stated. No significant differences in baseline demographics between the 2 groups<br>**Inclusion criteria**<br>1. Demonstrating ADHD symptoms in serious and persistent form, agreed by parents and teachers<br>2. Symptoms present for ≥ 12 months (parents to verify)<br>3. Meeting criteria for ADD including hyperactivity<br>4. According to DSM-III<br>5. Reading deficit of ≥ 2 grade levels<br>**Exclusion criteria**<br>1. Symptoms seem to stem from stress at home or from inconsistent child management<br>2. No major diseases or obvious physical defects (gross neurological, sensory, motor impairment or psychosis) |
| Interventions | Participants were randomly assigned to methylphenidate + cognitive training or to cognitive training only<br>Mean methylphenidate dosage: 0.3 mg/kg (range 5 mg/d to 15 mg/d)<br>Administration schedule: twice daily (morning and lunch)<br>Duration of intervention: 12 weeks + 3 months (only with medication)<br>Titration period: none<br>Treatment compliance: not stated<br>Cognitive training programme: individual, twice-weekly, 1-hour sessions for a total of 24 sessions spanning a 3-month period |
| Outcomes | **ADHD symptoms**<br>1. Conners' Parent Rating Scale and Conners' Abbreviated Teacher Rating Scale: baseline, 12 weeks, 3 months<br>2. Teacher Rating of Attention: baseline, 12 weeks, 3 months<br>3. Teacher Rating of Impulsivity: baseline, 12 weeks, 3 months |
| Notes | Sample calculation: no<br>Ethics approval: no information<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Key conclusion of study authors**<br>1. Children in the 2 medication treatment conditions demonstrated improvement in attentional deployment and in behavioural ratings |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomly assigned |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | High risk | Open-label methylphenidate |
| Blinding of outcome assessment (detection bias) | High risk | Not blinded |
| Incomplete outcome data (attrition bias) | Low risk | All participants followed up |
| Selective reporting (reporting bias) | Low risk | No protocol/design published. All pre-specified outcomes of interest have been reported |
| Vested interest bias | Low risk | Funding: research supported by US Public Health Services Grant from the National Institute of Mental Health (NIMH), and by the Biomedical Research Award from the National Institutes of Health (NIH). Methylphenidate provided by CIBA-GEIGY Corporation, Summit, New Jersey<br>Conflicts of interest: not stated |

*Brown 1988*

| Methods | Eight-week, double-blind, randomised, cross-over trial with 4 interventions<br>1. Placebo<br>2. 0.15 mg/kg methylphenidate<br>3. 0.30 mg/kg methylphenidate<br>4. 0.5 mg/kg methylphenidate |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 11 (all boys). Participants were randomly assigned to possible drug condition orders<br>Number of participants followed up: 11<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-III (subtype not stated)<br>Age: mean 13 years, 7 months (range 12 years and 10 months to 14 years and 10 months)<br>IQ: full-scale mean 92.91 (range 86 to 104)<br>Methylphenidate naive: not stated, but none of the participants had been treated with stimulants during the year preceding the study<br>Ethnicity: African American (100%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: conduct disorder, socialised aggressive (45%)<br>Comedication: no<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Sexual rating of ≥ 3 according to Tanner's classification of stages of development, to ensure post-pubertal status<br>2. ADD according to DSM-III<br>3. Score of ≥ 15 on the Abbreviated Conners' Teacher Rating Scale<br>**Exclusion criterion**<br>1. Mental retardation or gross neurological disorders |
| Interventions | Interventions (mean dosage)<br>1. Placebo<br>2. Methylphenidate low (0.15 mg/kg)<br>3. Methylphenidate medium (0.30 mg/kg)<br>4. Methylphenidate high (0.5 mg/kg)<br>Mean methylphenidate dosage: methylphenidate low (4.38 mg), medium (12.55 mg), high (21.28 mg)<br>Administration schedule: twice daily; morning and noon<br>Duration of each medication condition: 2 weeks<br>Washout before study initiation: none (but no stimulant treatment for the past year)<br>Titration period: none<br>Treatment compliance: Compliance was determined to be satisfactory |

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| Outcomes | **ADHD symptoms**<br>At the end of each 2-week trial, parents and teachers completed the following rating scales<br>1. Conners' Parent Rating Scale - Revised<br>2. Abbreviated Conners' Parent Hyperactivity Index<br>3. Abbreviated Conners' Teacher Hyperactivity Index<br>4. ADD/H Comprehensive Teacher Rating Scale<br>**Non-serious adverse events**<br>1. Side Effects Rating Scale (includes questions about sleep disturbances, dysphoria, decreased appetite, physiological complaints such as headaches and generalised anxiety), parent-rated (assessing the preceding week)<br>2. Cardiovascular measures (heart rate, resting systolic and diastolic measures for blood pressure) assessed ≥ 1 hour after administration of methylphenidate or placebo. Apical pulse rates taken for 1 full minute<br>3. Weight (during every clinic visit) |
| Notes | Sample calculation: no<br>Ethics approval: yes; Institutional Review Board (IRB) at Emory University<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Key conclusion of study authors**<br>1. Significant drug effects were found for most measures. In general, higher doses resulted in the most beneficial response in behavioural, academic and laboratory measures of attention and impulsivity. However, a significant linear increase occurred in diastolic blood pressure. Results suggest that methylphenidate is an effective adjunct to the treatment of ADD in adolescents<br>**Comment from study authors**<br>1. We do not know whether our findings can be generalised in non-black populations<br>Email correspondence with study authors: October 2013. We received from study authors additional information about ethics approval, planned outcomes and participants followed up. Unfortunately, it was not possible for study authors to provide other data that we needed because the study was conducted many years ago, and study authors no longer had the data |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Drug order was randomly assigned across participants; no further description |
| Allocation concealment (selection bias) | Low risk | All medication was prepared in identical capsules by hospital pharmacists. Medication was dispensed in dated envelopes |
| Blinding of participants and personnel (performance bias) | Low risk | All medication was prepared in identical capsules by hospital pharmacists. Medication was dispensed in dated envelopes. Double-blind |
| Blinding of outcome assessment (detection bias) | Unclear risk | Double-blind |
| Incomplete outcome data (attrition bias) | Low risk | No withdrawals<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Low risk | Researchers administered all measures that were proposed and reported these data in the published report |
| Vested interest bias | Low risk | Biomedical Research Support Grant Program, Division of Research Resources, National Institutes of Health and Emory University Research<br>Conflicts of interest: none reported |

*Brown 1991*

| Methods | Double-blind, randomised, cross-over trial with 2 interventions<br>1. Methylphenidate<br>2. Placebo<br>Phases: methylphenidate 10 mg, methylphenidate 15 mg, methylphenidate 20 mg, placebo |
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| Participants | Study consisted of 22 participants, but only 7 had ADD. As outcomes were reported separately for these 7 participants, we were able to include the study<br>Number of participants screened: 25<br>Number of participants included: 22 (all boys). Participants were randomly assigned to 1 of 4 possible drug condition orders (in counterbalanced order)<br>Number of participants followed up: 22<br>Number of withdrawals: 0<br>Diagnosis: DSM-III (conduct disorder, with 7 of 22 also diagnosed with ADD)<br>Age: mean:15.8 years (range 12.9 to18.9)<br>IQ: 96.22 (SD 15.12, range 80 to 123)<br>Methylphenidate naive: not stated<br>Ethnicity: Caucasian (100%)<br>Country: USA<br>Setting: hospital/out-patient clinic<br>Comorbidity: conduct disorder (100%)<br>Comedication: no<br>Sociodemographics: middle and upper-middle class<br>**Inclusion criterion**<br>1. Hospitalised adolescents diagnosed with conduct disorder<br>**Exclusion criterion**<br>1. Mental retardation, psychosis and organic brain disorder |
| Interventions | Participants were randomly assigned to 1 of 4 possible drug condition orders of methylphenidate (10 mg, 15 mg, 20 mg) and placebo<br>Mean methylphenidate dosage: 0.15 mg/kg, 0.22 mg/kg and 0.31 mg/kg<br>Administration schedule: twice daily, 8:00 AM and 12:00 PM<br>Duration of each medication condition: 4 days<br>Washout before study initiation: not stated<br>Titration period: 1 day before first phase<br>Treatment compliance: 100% |
| Outcomes | **General behaviour**<br>1. Conners' Teacher Rating Scale (conduct factor): teacher-rated daily<br>**Non-serious adverse events**<br>1. Side Effects Rating Scale (including 17 known adverse events for methylphenidate): observer-rated daily<br>2. Cadiovascular measures were recorded 90 minutes after 12:00 PM administration |

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| **Notes** | Sample calculation: not stated<br>Ethics approval: not stated<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; initially participants received a 1-day open trial of methylphenidate. Three participants were excluded because of intolerability<br>**Comments from study authors**<br>1. ... in our study, mean milligram per kilogram doses were lower than in previously published reports … doses may simply have been too small to induce any real change in behaviour<br>2. Another limitation that may have influenced the results is timing of the measurements of behaviour. As behavioural ratings were made by teachers at the end of the day, it is possible that medication effects (particularly for lower doses) had dissipated by the time the ratings were made<br>**Key conclusions of study authors**<br>1. In summary, results are of theoretical importance and with additional research may suggest the potential efficacy of stimulants for treating adolescents with conduct disorders in the absence of ADD<br>2. The present data may be interpreted to suggest that ADD may be managed with stimulant medication when it presents comorbidly with conduct disorder<br>**Comment from review authors**<br>1. Data on the conduct disorder + ADD group were reported separately in the study - that is why we could use the data<br>Email correspondence with study authors: unable to locate contact details for study authors |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | All participants received each of the 4 doses in 1 of 24 possible randomly assigned sequences |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Low risk | Methylphenidate and placebo were packaged in coloured gelatin capsules by the hospital pharmacist to avoid detection of dose, visually or by taste |
| Blinding of outcome assessment (detection bias) | Low risk | Under double-blinded conditions |
| Incomplete outcome data (attrition bias) | Low risk | All participants followed up |
| Selective reporting (reporting bias) | Unclear risk | No protocol published. Not all pre-specified outcomes of interest have been reported (e.g. scores on Conners' Teacher Rating Scale) |
| Vested interest bias | Unclear risk | Conflicts of interest: not stated |

***Buitelaar 1995***

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| **Methods** | Randomised, cross-over trial with 3 interventions<br>1. Pindolol<br>2. Methylphenidate<br>3. Placebo<br>**Phases**<br>1. Phase 1: 4-week treatment block<br>2. Phase 2: 2-week drug-free interval<br>3. Phase 3: 4-week treatment block<br>First 32 participants were randomly assigned to interventions 1 to 3 in the first treatment block, and to intervention 1 or 2 in the second treatment block. Next 20 participants were randomly assigned to intervention 2 or 3 in the first treatment block, and to intervention 2 or 3 in the second treatment block |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 52 (46 boys, 6 girls); however, because of an incomplete block design, only 46 were treated with methylphenidate and 31 were treated with placebo in first or second treatment block<br>Number of participants followed up: 52<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-III-R (subtype not stated)<br>Age: mean 9.3 years (range 6 to 13)<br>IQ: mean 94.2<br>Methylphenidate naive: 100%<br>Ethnicity: not stated<br>Country: the Netherlands<br>Setting: out-patient clinic<br>Comorbidity: conduct disorder (38%); depressive disorder, dysthymia or major depressive disorder (15%); anxiety disorder, overanxious disorder or avoidant disorder (42%); psychomotor epilepsy (2%)<br>Comedication: antiepileptic medication (carbamazepine) at a fixed dosage (2%)<br>Sociodemographics: 20% were from families of high socioeconomic status, 50% of middle socioeconomic status and 30% of low socioeconomic status (on the Hollingshead Index). No significant difference in baseline characteristics were noted between groups of children treated with methylphenidate, pindolol or placebo<br>**Inclusion criteria**<br>1. ADHD according to DSM-III-R criteria<br>2. Scores in the clinical range on both the Child Behavior Checklist and Conners' Teacher Rating Scale, Hyperactivity factors<br>3. Deficits in attention performance on a reaction time task or a continuous performance task in neuropsychological testing<br>4. No previous treatment with psychotropic medication<br>5. Clinical indication for drug treatment<br>**Exclusion criteria**<br>1. Diagnosis of tic disorder or pervasive developmental disorder<br>2. Family history of tic disorder<br>3. Contraindications to treatment with blockers such as cardiac disease, in particular, conduction abnormalities and bradycardia, hypotension, obstructive pulmonary disease and insulin-dependent diabetes |

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| Interventions | Participants were randomly assigned to possible drug condition orders of 40 mg pindolol, 20 mg methylphenidate and placebo<br>Fixed dosage: 10 mg methylphenidate, twice daily (approximately 0.6 mg/kg/d)<br>Administration schedule: morning and noon<br>Duration of each medication condition: 4 weeks<br>Washout before study initiation: no (medication naive)<br>Medication-free period between interventions: 2 weeks<br>Titration period: yes. After randomisation, during the first 3 days of a treatment period, participants received 1 morning dose (10 mg methylphenidate, 20 mg pindolol or placebo). After completion of endpoint assessment, medication was tapered off (3 days with 1 morning dose)<br>Treatment compliance: good to very good in 96% of children. Two children had poor compliance under methylphenidate treatment as the result of side effects |
| Outcomes | **ADHD symptoms**<br>1. 10-Item Abbreviated Conners' Rating Scale: rated by parents, teachers and a psychologist<br>2. 93-Item Conners' Parents Rating Scale<br>3. 39-Item Conners' Teachers Rating Scale<br>Parents and teachers completed ratings at baseline, at week 2 and at endpoint of each treatment period. The psychologist completed ratings at baseline and at endpoint of each treatment period. Furthermore, ACRS was rated 30 minutes after drug administration<br>**Non-serious adverse events**<br>1. Adverse effects checklist (encompassing 20 possible side effects, modified from the Stimulant Drug Side Effects Rating Scale, rated by parents after 2 and 4 weeks of treatment<br>2. Treatment-emergent adverse effects were further assessed systematically at endpoint by research psychiatrist<br>3. Pulse and blood pressures were recorded at each clinical visit |

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| Notes | Sample calculation: yes; for comparison of pindolol with methylphenidate (50 participants)<br><br>Ethics approval: yes; approved by the Committee for Research on Human Subjects of Utrecht University Hospital<br><br>**Comments from study authors**<br><br>1. Interim analysis of side effects indicated that pindolol was associated with significantly more intense adverse effects when compared with placebo and methylphenidate. Consequently, pindolol was dropped from the study design, and the next 20 participants were included in a randomised methylphenidate-placebo cross-over design<br>2. Study was limited by use of fixed dosage, with exclusive focus on behavioural symptoms - not on improvement in neuropsychological measures of information processing, and with an incomplete and unbalanced block design<br><br>**Key conclusions of study authors**<br><br>1. Beta-blocker pindolol appeared to be modestly effective in the treatment of behavioural symptoms of children with ADHD. Data suggest some utility for pindolol in treating hyperactivity and conduct problems in children with ADHD, but safety concerns about troubling side effects clearly limit use of pindolol in ADHD<br>2. Only strong levels of response could be predicted by baseline characteristics. Severity of disorder based on clinical judgement and improvement after a single dose of methylphenidate are found to be important contributors to response prediction<br><br>**Comments from review authors**<br><br>1. Study designed to compare usage of pindolol and methylphenidate<br>2. Few participants<br>3. Study design changed during the study because of adverse effects. Phase 2 changed intervention from pindolol versus methylphenidate to methylphenidate versus placebo<br>4. Phase 1: Given the relatively small sample sizes, effects of single treatments (i.e. methylphenidate vs placebo, and pindolol vs placebo) were not robust enough to reach conventional levels of statistical significance<br><br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no; only medication-naive participants<br><br>Any withdrawals due to adverse events: no; however, in 4 participants, dosages of methylphenidate had to be adjusted in the first 2 weeks of the study because of increased agitation, restlessness and insomnia. Two participants remained on 5 mg of methylphenidate for 4 weeks, whereas dosage for the other 2 participants could be gradually increased to 10 mg methylphenidate in the last 2 weeks<br><br>Email correspondence with study authors: January to March 2014. Requested but did not receive from study authors supplemental efficacy and safety data and information regarding randomisation, allocation concealment and blinding |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomly assigned, not further described |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | Double-blind, not further described. Methylphenidate and placebo were administered in identical-looking tablets |
| Blinding of outcome assessment (detection bias) | Unclear risk | Double-blind |
| Incomplete outcome data (attrition bias) | Low risk | Two participants from the methylphenidate group had bad compliance but were included in the analyses, as an ITT analysis was planned<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no, but design of study changed during the course of the study because of adverse events |
| Selective reporting (reporting bias) | Unclear risk | Protocol not identified |
| Vested interest bias | Unclear risk | Not stated<br>Conflicts of interest: no affiliations with pharmaceutical companies stated |

### *Bukstein 1998*

| Methods | Cross-over trial with 3 interventions<br>1. Methylphenidate 0.3 mg MPH/kg<br>2. Methylphenidate 0.6 mg MPH/kg<br>3. Placebo<br>Phases: Study included 2 phases: a baseline phase and the medication trial itself. The baseline phase occurred during the first 2 weeks (9 days) of the programme, when the children were medication-free. Each medication condition was administered for 7 days of the programme during the 21-day trial |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 18. Participants were randomly assigned to 1 of 3 possible drug condition orders<br>Number of participants followed up: 18 (14 boys, 4 girls)<br>Number of withdrawals: 0<br>DSM-III-R criteria for ADHD and oppositional defiant disorder or conduct disorder<br>Age: mean 9.4 years (range 6.1 to 12.2)<br>IQ: not stated<br>Methylphenidate naive: not stated<br>Ethnicity: Caucasian (17%), African American (83%)<br>Country: USA<br>Setting: out-patient clinic (summer school at clinic)<br>Comorbidity: oppositional defiant disorder (56%) and conduct disorder (44%)<br>Comedication: no<br>Sociodemographics: Participants were predominantly from lower socioeconomic classes, with an average Hollingshead Index of Social Status of 3.83 (SD 1.65, range 1 to 5). Thirteen (72%) of the participants' families were receiving public assistance. Only 4 of the children lived with both biological parents; 12 (67%) lived with their biological mother only. Inner city environment characterised by higher than average rates of poverty and community violence. No significant differences in baseline demographics between groups<br>**Inclusion criterion**<br>1. DSM-III criteria for ADHD and oppositional defiant disorder or conduct disorder, while attending the Summer Treatment and Enrichment Program (STEP)<br>**Exclusion criterion**<br>1. Not stated |
| Interventions | Participants were randomly assigned to 1 of 6 possible drug condition orders of methylphenidate (0.3 mg/kg or 0.6 mg/kg) and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: 8:30 AM, 11:45 AM and 3:00 PM<br>Duration of each medication condition: 7 days<br>Washout before study initiation: 9 days<br>Medication-free period between interventions: none<br>Titration period: none<br>Treatment compliance: poor compliance with the weekend medication condition; most families missed ≥ 1 dose each weekend of the trial. Poor compliance with the 3-dose regimen was so widespread that trialists omitted from the trial all data on weekend doses |
| Outcomes | **ADHD symptoms**<br>1. IOWA Conners' Rating Scale: rated by staff daily<br>2. IOWA Conners' Parent Rating Scale: rated by parents daily<br>3. Conners' Teacher Rating Scale: rated daily<br>**Non-serious adverse event**<br>1. Side Effects Rating Scale: adaptation of the Barkley Side Effects Rating Scale, rated daily by staff and also rated by parents |

| Notes | Key conclusions of study authors<br>1. Staff ratings of behaviour of children in the programme and in an academic classroom showed that children displayed significant improvement in ADHD symptoms and aggressive behaviour with low- and high-dose methylphenidate conditions<br>2. At home, parents and guardians reported few significant differences in behaviour ratings between placebo and methylphenidate<br>3. In both settings, methylphenidate was well tolerated, with few side effects found during active drug conditions<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: no |
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Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Schedule for each condition was randomly assigned across the 5 weekdays to minimise programme effects; the only qualifying condition was that approximately one-half of the 7 days of each medication condition would occur during each half of the 21-day trial |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | Nurse and other Summer Treatment and Enrichment Program (STEP) staff, children and parents were blinded to dosages and schedules |
| Blinding of outcome assessment (detection bias) | Low risk | Each child's daily data were collected and entered by trained research associates, who were unaware of medication status |
| Incomplete outcome data (attrition bias) | Low risk | All included in the analyses |
| Selective reporting (reporting bias) | Unclear risk | No protocol identified |
| Vested interest bias | Low risk | None |

### *Butter 1983*

| Methods | One-week, double-blind, parallel trial with 3 arms<br>1. Adrenocorticotropic hormone<br>2. Methylphenidate (10 mg, 15 mg or 20 mg, weight adjusted)<br>3. Placebo |
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|---|---|
| Participants | Number of participants screened: not stated<br>Number of participants included: 30 (all boys)<br>Number of participants randomly assigned: methylphenidate 10, placebo 10<br>Number of participants followed up: methylphenidate 10, placebo 10<br>Diagnosis of ADHD: DSM-III<br>Age: mean in years (range 6 to 12)<br>IQ: above 85<br>Methylphenidate naive: not stated<br>Ethnicity: not stated<br>Country: Canada<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated. No information about significant differences in baseline demographics between groups<br>**Inclusion criteria**<br>1. Clinical ADHD diagnosis of attention deficit disorder with hyperkinesis (DSM-III)<br>2. Hyperkinesis rating required a score of 15 or higher on Conners' Short Form Rating Scale, and hyperkinetic behaviour had to be apparent throughout most of the day<br>3. Untreated behaviour had to be a cause of severe difficulty both at home and at school<br>**Exclusion criterion**<br>1. Wechsler Intelligence Scale for Children (WISC) score < 85 or abnormal perceptual functioning |
| Interventions | Participants were randomly assigned to adrenocorticotropic hormone, methylphenidate or placebo<br>Mean methylphenidate dosage: 0.5 mg/kg<br>Administration schedule: once daily, 7.30 AM<br>Duration of intervention: 1 week. One week drug-free followed by 1 week of placebo treatment. After placebo washout, randomly assigned to adrenocorticotropic hormone, methylphenidate or placebo<br>Titration period: none<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. Conners' Short Form Rating Scale: completed by parents and clinicians<br>2. Conners' Rating Scale Teachers: rated during placebo and active drug phases<br>**Non-serious adverse event**<br>1. EEG, haematology, liver and kidney function test, blood pressure and pulse, blood chemistry, urinalysis before and after treatment<br>EEG, haematology, blood chemistry and urinalysis were within normal limits before treatment and remained so after treatment |

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| **Notes** | Sample calculation: not stated<br>Ethics approval: not stated<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Key conclusion of study authors**<br>1. Children treated with methylphenidate show significantly greater vasomotor reactivity, behavioural improvement and learning receptivity than children treated with adrenocorticotropic hormone and placebo |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | After placebo washout, treatment was assigned in a double-blind and random manner |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | Described as double-blind |
| Blinding of outcome assessment (detection bias) | Unclear risk | Neurologist assessing EEG blinded. Double-blind |
| Incomplete outcome data (attrition bias) | Low risk | No drop-outs<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Unclear risk | No information |
| Vested interest bias | Low risk | Funded by the Scientific Development Group, Organon International B.V., Oss, the Netherlands<br>Conflicts of interest: none |

### *Carlson 1995*

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|---|---|
| **Methods** | Double-blind, placebo-controlled, repeat-measures (across drug and dosage), cross-over trial with 6 interventions<br>1. Methylphenidate at 10 mg twice daily<br>2. Methylphenidate at 15 mg twice daily<br>3. Methylphenidate at 20 mg twice daily<br>4. Desipramine alone<br>5. Desipramine + methylphenidate<br>6. Placebo<br>Phases: Each child received placebo, desipramine, each of the 3 doses of methylphenidate (10 mg, 15 mg, 20 mg) and combined desipramine and methylphenidate (at the same 3 doses) |

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| Participants | Number of participants screened: not stated<br>Number of participants included: 16 (all boys). Participants were randomly assigned to different drug condition orders and placebo<br>Number of participants followed up: 16<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-IV (combined (62.5%), inattentive (12.5%), “in partial remission” (25%))<br>Age: mean: not reported (range 7.9 to 12.10 years)<br>IQ: mean not stated (range overall 81 to 121; range verbal 74 to 113, range performance 73 to 126)<br>Methylphenidate naive: 4 (25%)<br>Ethnicity: Caucasian (87.5%), African American (12.5%)<br>Country: USA<br>Setting: in-patient ward<br>Comorbidity: yes; major depressive disorder (68.75%), dysthymic disorder (31.25%). “All had ODD, CD or both”<br>Comedication: yes<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Initial team diagnosis of ADHD, non-bipolar major depressive disorder, dysthymic disorder or a combination thereof<br>2. ≥ 7 years old<br>3. Wechsler Intelligence Scale for Children, Revised, full-scale IQ > 80<br>**Exclusion criteria**<br>1. Medical contraindication to medications being investigated<br>2. Family history of bipolar disorder in first- or second-degree relatives<br>3. Abnormal baseline laboratory values or ECG |
| Interventions | Participants were randomly assigned to different possible drug condition orders of methylphenidate (10 mg, 15 mg and 20 mg), twice daily at 7:30 AM and 11:30 AM × 6 days, then 1-day washout; the titrated therapeutic level (125 ng/mL to 225 ng/mL) of desipramine twice daily at 3:30 PM and 7: 30 PM × 3 weeks minimum before final measures taken; and placebo<br>Mean methylphenidate dosage: not stated<br>Duration of each medication condition: 1 week<br>Washout before study initiation: 14 days<br>Medication-free period between intervention: 1 day<br>Titration period: none<br>Treatment compliance: not stated |

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|---|---|
| Outcomes | **ADHD symptoms**<br>1. ADD/H Comprehensive Teacher Rating Scale (ACTerRS): teacher-rated<br>**General behaviour**<br>1. Humphrey's Teacher Self-Control Rating Scale<br>2. Inpatient Global Rating Scale<br>**Non-serious adverse events**<br>1. Subjective Treatment Emergent Symptom Scale: side effect ratings, collected weekly by nurse<br>2. Somatic factor of the Inpatient Global Rating Scale: collected weekly by nurse<br>3. Childrens' Depression Rating Scale - Revised: Appetite and Sleep disturbance items collected weekly by research psychologist<br>4. Cardiovascular side effects (daily morning blood pressure and pulse rates + weekly ECG) |
| Notes | Sample calculation: not stated<br>Ethics approval: not stated<br>**Key conclusion of study authors**<br>1. "With regard to differential efficacy, the major findings of this study were that a combination of MMI and MPH (at 20 mg) was somewhat more effective than DMI or MPH alone for improving hyperactive, inattentive and oppositional defiant, and 'aggressive' behaviours across both school and unit settings. Efficacy was also demonstrated for MPH and DMI alone in school, but less so on the unit"<br>**Comment from review authors**<br>1. Small sample of 16 participants entering the trial seems heterogeneous and opportunistic rather than clearly defined, with a mixture of diagnoses including mood, ADHD and oppositional defiant disorder/conduct disorder. This makes it difficult to believe that the results are reliable<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: maybe; hence exclusion criterion number 1: medical contraindication to medications being investigated<br>Email correspondence with study authors. Emailed first study author to ask for outcome data in mean and SD format. Study authors replied in July 2014 to say that they were unable to help us |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | High risk | Not stated |
| Allocation concealment (selection bias) | High risk | Not stated |
| Blinding of participants and personnel (performance bias) | Low risk | Medications were packaged in identical grey capsules (size 00) that were administered 4 times per day |
| Blinding of outcome assessment (detection bias) | Low risk | For this protocol, all raters (including teachers, nurses, psychologist and physicians, except for the attending child psychiatrist, who controlled the desipramine dosage but did not rate the children), children and parents were blinded to all medication conditions |
| Incomplete outcome data (attrition bias) | Unclear risk | Not stated |
| Selective reporting (reporting bias) | Unclear risk | Not stated |
| Vested interest bias | Unclear risk | Not stated |

*Carlson 2007*

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|---|---|
| Methods | Six-week, multi-centre, double-blind, parallel, randomised controlled trial (RCT) with 2 arms<br>1. Atomoxetine + methylphenidate<br>2. Atomoxetine + placebo<br>RCT was preceded by a 4-week, open-label, atomoxetine and placebo phase, during which participants who had adequate response were removed |

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| Participants | Number of participants screened: not stated<br>Number of participants included: phase 1 (4-week open-label atomoxetine and placebo phase) 25 (1 boy, 20 girls); phase 2 (6-week, double-blind RCT) 17<br>Number of participants randomly assigned: methylphenidate 9, placebo 8<br>Number of participants followed up: methylphenidate 8, placebo 7<br>Number of withdrawals: methylphenidate 1, placebo 1<br>Diagnosis of ADHD: DSM-IV (combined (79% in phase 1))<br>Age: phase 1 mean 9.6 years (range 6 to 12)<br>IQ: > 70<br>Stimulant-naive: 4%<br>Ethnicity: Caucasian (83%), other (17%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder (50% in phase 1)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria, including assessment details**<br>1. 6 to 12 years of age<br>2. DSM-IV diagnosis of ADHD, any type<br>3. Rating on ADHD Rating Scale, Fourth Edition, Parent Version - Investigator Administered and Scored Version of ≥ 1.5 SD above age and sex norms<br>4. Severity rating of at least moderate on the Clinical Global Impressions Severity Scale<br>5. History (preceding 12 months) of insufficient response to an adequate stimulant trial, which was defined as gradual titration of stimulant medication for ≥ 2 weeks at specified doses for each medication. Inadequate response was determined by the child's prescribing physician, who also documented his or her opinion that a change in treatment was needed<br>6. Patients must be of normal intelligence, as assessed by the investigator (i.e. without a general impairment of intelligence, and likely, in the investigator's judgement, to achieve a score ≥ 70 on an IQ test) (Administration of a formal IQ test is not an entry requirement for this study. Specific learning disabilities are not considered general impairments of intelligence)<br>7. Patients must be able to swallow capsules<br>**Exclusion criteria**<br>1. Weighed < 22 kg or > 60 kg at study entry<br>2. Had any other Axis I diagnosis, including pervasive developmental disorder, mood or anxiety disorder (Presence of comorbid oppositional defiant disorder was not an exclusion criterion)<br>3. Bipolar disorder, autism<br>4. Any medical conditions that would contraindicate the use of atomoxetine or extended-release methylphenidate<br>5. History of any seizure disorder and/or Rolandic seizures (other than febrile seizures) or prior ECG abnormalities in the absence of seizures, or history of taking (or are currently taking) anticonvulsants for seizure control<br>6. History of severe allergies to > 1 class of medication or multiple adverse drug reactions, including hypersensitivity to methylphenidate<br>7. History of intolerance or non-response to atomoxetine<br>8. Used any concomitant psychotropic or excluded medications<br>9. Ingestion of any excluded medications 5 days before baseline ratings and randomisation |

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| Interventions | Participants were randomly assigned to extended-release OROS methylphenidate or placebo<br>Cointervention: atomoxetine<br>Methylphenidate mean dosage: 1.02 mg/kg<br>Administration schedule: once daily<br>Duration of intervention: 6 weeks<br>Titration period for methylphenidate: after randomisation to target dose of 1.08 mg/kg/d (max 1.2 mg/kg/d)<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. ADHD Rating Scale, Fourth Edition, Parent Version - Investigator Administered and scores: parent-rated<br>2. Conners' Parent Rating Scale Revised, Short Form: parent-rated at baseline and at weeks 4, 5, 6 and 10<br>**General behaviour**<br>1. Weekly Parent Ratings of Evening and Morning Behaviour: parent-rated at baseline and at weeks 4, 5, 6 and 10<br>**Non-serious adverse events**<br>1. Vital signs, at each visit<br>2. Weight, at each visit<br>3. Spontaneous adverse event reports, at each visit |
| Notes | Sample calculation: Included sample (25 participants) is too small in relation to the sample calculation (85 participants)<br>Ethics approval: yes<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no, but exclusion of atomoxetine/placebo responders before study phase 2<br>**Comment from study authors**<br>1. The present findings can be applied only to children with an inadequate stimulant response. Given the small study sample, particularly in the combination treatment groups, the findings must be considered preliminary<br>**Key conclusion of study authors**<br>1. Methylphenidate appears to be safely combined with atomoxetine, but conclusions are limited by small sample<br>**Comment from review authors**<br>1. For the review, we used data from study phase 2, that is, the RCT with 2 arms (intervention: methylphenidate + atomoxetine; control: placebo + atomoxetine)<br>Email correspondence with study authors. June to November 2013. We received from study authors and sponsoring pharmaceutical company, supplemental information regarding IQ and blinding procedures, as well as data on weight, treatment-emergent adverse events and ECG |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomly assigned via an interactive voice response system to receive extended-release methylphenidate or placebo |
| Allocation concealment (selection bias) | Low risk | Investigators and participants were blinded to the precise visit at which randomisation to blinded placebo or Concerta occurred, as this visit is not identified in the investigator's copy of the protocol, and as use of blinded study drug begins at visit 2 and continues up to visit 8 |
| Blinding of participants and personnel (performance bias) | Low risk | Double-blind |
| Blinding of outcome assessment (detection bias) | Low risk | Double-blind |
| Incomplete outcome data (attrition bias) | Low risk | Efficacy outcome measures were conducted on the ITT sample by using an LOCF method<br>Selection bias: no |
| Selective reporting (reporting bias) | Low risk | Protocol identified |
| Vested interest bias | High risk | Funding: Research was funded by Eli Lilly and Company, Indianapolis, Indiana<br>Conflicts of interest: Dr. Carlson has received research support or has consulted with the following companies: Abbott Laboratories, Cephalon, Eli Lilly and Company, Janssen, McNeil, Otsuka and Shire Pharmaceuticals. Dr. Dunn has received research support or has served on Speakers' Bureaus of the following companies: AstraZeneca, Eli Lilly and Company, NIH, Otsuka and Pfizer Pharmaceuticals. Drs. Kelsey, Ruff, Ball and Allen and Ms. Ahrbecker are employees and/or shareholders of Eli Lilly and Company |

*Castellanos 1997*

| Methods | Nine-week, double-blind, cross-over trial with 3 interventions for 3 weeks each<br>1. Methylphenidate<br>2. Dextroamphetamine<br>3. Placebo<br>Study was followed up by an open clinical follow-up of 22 months |
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| Participants | Number of participants screened: 64<br>Number of participants included: 22 (all boys). Participants were randomly assigned to different possible drug condition orders<br>Number of participants followed up: 20<br>Number of withdrawals: 2<br>Diagnosis of ADHD: DSM-III-R<br>Age: mean 9.4 years (range 6 to 13)<br>IQ: mean 98.8<br>Methylphenidate naive: 0<br>Ethnicity: Caucasian (80%), African American (10%), Asian (5%), Hispanic (5%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: Tourette's disorder (95%), chronic motor tics (5%), conduct disorder (5%), oppositional defiant disorder (30%), reading disorder (5%), overanxious disorder (5%), obsessive-compulsive disorder (10%), enuresis (20%)<br>Comedication: 4 received haloperidol<br>Sociodemographics: no information<br>**Inclusion criteria**<br>1. DSM-III criteria for Tourette's disorder, with tics confirmed by a knowledgeable clinician ≥ 1 year before referral<br>2. Symptoms of ADHD present in ≥ 2 settings<br>3. Conners' hyperactivity factor scores from home teacher ≥ 2 SD > age norms<br>**Exclusion criteria**<br>1. Full-scale IQ < 75 (Wechsler Intelligence Scale for Children - Revised)<br>2. Evidence of medical or neurological disease<br>3. Any other Axis I psychiatric disorder except obsessive-compulsive disorder, conduct or oppositional disorder, overanxious disorder and specific developmental disorders |
| Interventions | Participants were randomly assigned to 1 of the possible drug condition orders of methylphenidate and placebo. Methylphenidate was increased weekly. For body weight > 30 kg, weekly methylphenidate doses were 15 mg/dose, 25 mg/dose and 45 mg/dose b.i.d. (for weight ≤30 kg, 12.5: 25 mg/dose and 45 mg/dose, b.i.d.)<br>Mean methylphenidate dosage: main cohort 1.20 mg/kg, second cohort 0.69 mg/kg, third cohort 1.22 mg/kg<br>Administration schedule: twice a day: breakfast and lunch<br>Duration of each medication condition: 3 weeks. First cohort underwent weekly increases in stimulant doses described as low, medium and high. Second cohort underwent increase described as low, medium and medium, and the third cohort as low, high and high<br>Washout before study initiation: minimum 4 weeks<br>Medication-free period between interventions: 20 hours<br>Titration period: during the first 3 weeks of intervention<br>Treatment compliance: no information |
| Outcomes | **ADHD symptoms**<br>1. Conners' Teacher Rating Scale: completed by day programme teachers, weekly ratings<br>**Non-serious adverse events**<br>1. Adverse effects<br>2. Tic severity: Unified Rating Scale (Tourette Syndrome Association): variety, frequency, intensity, complexity and interference of motor and vocal tics based on observations by programme staff and derived by consensus at weekly meetings |

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| **Notes** | Sample calculation: no<br><br>Ethics approval: approved by the National Institute of Mental Health (NIMH) Institutional Review Board<br><br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br><br>**Comments from study authors**<br><br>1. Limitations<br>a. Small sample size<br>b. Drug dosage was not randomly assigned<br>c. Allowed 4 participants to continue on a constant dose of haloperidol<br>d. Exploration of different dose schedules<br>e. As methylphenidate undergoes much more rapid and complete metabolism than dextroamphetamine, we would expect blood level curves of the 2 stimulants to differ markedly<br><br>**Key conclusion of study authors**<br><br>1. Substantial minority of comorbid participants had consistent worsening of tics while taking stimulants, although most experienced improvement in ADHD symptoms with acceptable effects on tics<br><br>**Comment from review authors**<br><br>1. Study consists of a main study of 12 boys followed by 2 smaller cohorts of, respectively, 6 and 4 boys<br><br>Email correspondence with study authors: January 2014. Corresponding author was not able to supply us with further information |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Participants were randomly assigned |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | Capsule formulation prepared by a pharmacy |
| Blinding of outcome assessment (detection bias) | Unclear risk | No information |
| Incomplete outcome data (attrition bias) | High risk | Two drop-outs; their data are not included in subsequent analyses. One of these was dropped from the study because of acute exacerbation of tics, and 1 because of excessively disruptive behaviour |
| Selective reporting (reporting bias) | High risk | Yes; they seem to have reported only hyperactivity scores from Conners' Teacher Rating Scale |
| Vested interest bias | Low risk | None declared<br><br>Conflicts of interest: not stated |

*Chacko 2005*

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|---|---|
| **Methods** | Six-week within-participant, randomised, placebo-controlled, double-blind, daily cross-over trial with 3 interventions<br>1. Methylphenidate at 0.3 mg/kg given at 7:45 AM and 11:45 AM<br>2. Methylphenidate at 0.6 mg/kg given at 7:45 AM and 11:45 AM<br>3. Placebo given at 7:45 AM and 11:45 AM<br>Phases: daily cross-over between medication conditions. Two weeks of baseline and adjustment period before 6-week medication trial. Data from this paper pertain to 5- and 6-year-old children attending a summer treatment programme between 1987 and 1997 |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 36 (32 boys, 4 girls). Participants were randomly assigned to 1 of 3 possible groups<br>Number of participants followed up: 36<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-III-R (n = 35, subtype not stated); DSM-IV (n = 1, combined type)<br>Age: mean 6.13 years (range 5 to 6)<br>IQ: mean 102 (SD 15.50)<br>Methylphenidate naive: not reported<br>Ethnicity: Caucasian (86%), other (14%)<br>Country: USA<br>Setting: out-patient clinic (summer treatment programme)<br>Comorbidity: oppositional defiant disorder (50%), conduct disorder (27.7%)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Diagnosis of ADHD according to DSM<br>2. Between 5 and 6 years of age<br>3. Parental consent<br>**Exclusion criteria**<br>1. None stated |
| **Interventions** | Participants were randomly assigned, daily, to 1 of 3 possible interventions: 0.3 mg/kg methylphenidate, 0.6 mg/kg methylphenidate and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: b.i.d. 7:45 AM and 11:45 AM from Monday through Thursday<br>Duration of each medication condition: daily shifted<br>Washout before study initiation: not stated<br>Medication-free period between interventions: maximum 18-hour gap between doses (11:45 AM to 7:45 AM the following day) and no medication Thursday to Sunday<br>Titration period: Before the 6-week trial began, participants underwent a 2-week baseline and adjustment period<br>Treatment compliance: not stated |

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| Outcomes | **Serious adverse events**<br>1. None reported<br>**Non-serious adverse events**<br>1. "Classroom teachers, counselors, and parents completed daily ratings of the presence and severity of common stimulant side effects"<br>Side effects are reported as occurring: "none" (i.e. symptom was assessed and was found absent), "mild" (i.e. symptom was present but was not sufficient to cause concern among child, peers or adults), "moderate" (i.e. symptom caused impairment of functioning or social embarrassment to the degree that benefits of medication must be considerable to justify risks of continuing medication) or "severe" (i.e. symptom caused significant impairment of functioning or social embarrassment to the degree that the child should not continue to receive medication). Rating of "moderate" or "severe" signifies clinically significant side effects. Side effects are based on staff/parent subjective report on severity of the side effect. Children were considered to have significant side effects in a particular area if clinically significant side effects were reported within that area for ≥ 50% of observations in a given condition |
| Notes | Sample calculation: no information<br>Ethics approval: no information<br>**Comments from study authors**<br>1. Study limitations. Most participants were white males, limiting the generalisability of findings to females and ethnic minorities<br>2. Furthermore, the sample size did not allow statistical analyses of ADHD subtype or comorbidity<br>**Key conclusion of study authors**<br>1. Stimulant medication is an effective treatment for young children diagnosed with ADHD; however, multiple domains of functioning must be assessed for the most effective dose for young children with ADHD to be determined<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: unclear; 2 weeks of adjustment period before the medication condition - no information on how many were screened and how many participated during baseline weeks<br>**Comments from review authors**<br>1. Participants in this study were attending a summer treatment programme between 1987 and 1997<br>2. Other articles from summer treatment programme<br>a. Pelham and Hoza, 1987<br>b. Pelham and Smith, 2000<br>c. Pelham and Hoza, 1996<br>d. Pelham et al., 1990<br>e. Pelham et al., 1993, 1999, 2002<br>Email correspondence with study authors: December 2013. We emailed study authors to request additional information about study sample and side effects. Study authors replied to say that the data are no longer available. Data from this study could not be used in meta-analyses |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "Active medication and placebo were disguised in opaque capsules and were dispensed in daily pill reminders. Each condition occurred one or two times per week, with the order of the conditions randomized on a daily basis. Data were averaged across days within conditions for each child" |
| Allocation concealment (selection bias) | Unclear risk | “Each condition occurred one or two times per week, with the order of the conditions randomized on a daily basis” |
| Blinding of participants and personnel (performance bias) | Low risk | “Active medication and placebo were disguised in opaque capsules and were dispensed in daily pill reminders”<br>Double-blinding |
| Blinding of outcome assessment (detection bias) | Unclear risk | Double-blinding |
| Incomplete outcome data (attrition bias) | Low risk | No drop-outs<br>Side effects were measured for 30 participants |
| Selective reporting (reporting bias) | High risk | Unclear how the population sample was selected from the group of attendees at these programmes over a 10-year period |
| Vested interest bias | High risk | During the conduct of this research, Dr. Pelham was supported by grants from the National Institute of Mental Health (NIMH) (MH48157, MH47390, MH45576, MH50467, MH53554, MH62946), NIAAA (AA06267, AA11873), National Institute on Drug Abuse (NIDA) (DA05605, DA12414), National Institute of Neurological Disorders and Stroke (NINDS) (NS39087), National Institute for Environmental Studies (NIES) (ES05015) and National Institute of Child Health and Human Development (NICHHD) (HD42080)<br>Conflicts of interest: Several study authors have affiliations with medical companies |

### *Childress 2009*

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| **Methods** | Five-week, multi-centre, multiple-setting, phase III, double-blind, randomised, placebo-controlled, parallel trial with 4 arms<br>1. Placebo<br>2. Extended-release dexmethylphenidate hydrochloride 10 mg<br>3. Extended-release dexmethylphenidate hydrochloride 20 mg<br>4. Extended-release dexmethylphenidate hydrochloride 30 mg<br>One to 3 weeks titration and 2 to 4 weeks maintenance period dependent on the allocated active drug group |
| **Participants** | Number of participants screened: 332<br>Number of participants included: 253 (163 boys, 90 girls)<br>Number of participants randomly assigned: extended-release dexmethylphenidate hydrochloride 188 (10 mg, n = 66; 20 mg, n = 62; 30 mg, n = 60), placebo 65<br>Number of participants followed up: extended-release dexmethylphenidate hydrochloride 161 (10 mg, n = 56; 20 mg, n = 54; 30 mg, n = 51), placebo 57<br>Number of withdrawals: extended-release dexmethylphenidate hydrochloride 27 (10 mg, n = 10; 20 mg, n = 8; 30 mg, n = 9), placebo 8<br>Diagnosis of ADHD: DSM-IV (combined (73.9%), hyperactive-impulsive (2.8%), inattentive (21.7%), missing data (1.6 %))<br>Age: mean 8.7 years (SD 1.84, range not reported)<br>IQ: not stated |

Methylphenidate naive: 69.2%

Ethnicity: Caucasian (57.7%), African American (28.9%), Asian (0.8%), other (12.6%)

Country: 34 centres in the United States

Setting: out-patient clinic

Comorbidity: respiratory, thoracic and mediastinal disorders (methylphenidate 26.9%, placebo 38.1%), immune system disorders (methylphenidate 22.5%, placebo 14.3%), nervous system disorders (methylphenidate 18.7%, placebo 19.0%), surgical and medical procedures (methylphenidate 15.4%, placebo 11.0%), infections and infestations (methylphenidate 14.3%, placebo 17.5%) and skin and subcutaneous tissue disorders (methylphenidate 11.0%, placebo 9.5%)

Comedication: ≥ 1 concomitant medication or non-drug therapy after start of study (methylphenidate 39.0%, placebo 44.4%). The most common concomitant medications were analgesics, antihistamines and allergy medications

Sociodemographics: not stated. Treatment groups were well balanced in relation to participant background characteristics, and baseline demographics were comparable among treatment groups

**Inclusion criteria**

1. 6 to 12 years of age
2. DSM-IV-TR diagnosis of ADHD
3. Patients attending school had to have the same teacher (English or Math) for the entire duration of the study, who was willing and able to spend sufficient time with the patient to make valid weekly assessments
4. Drug naive or not treated with any methylphenidate-related medication during the month before the study
5. Patients receiving psychological or behavioural therapies before the screening visit were considered eligible to participate, provided that therapy had been ongoing for ≥ 3 months with the same therapist
6. Patients had to have academic competence appropriate to their age and the following subscale total scores on Conners' ADHD/DSM-IV Scales - Teacher Version: For boys, baseline scores on Conners' ADHD/DSM-IV Scales - Teacher Version, Total subscale were required to be 27 for those 6 to 8 years old, 24 for those 9 to 11 years old and 19 for those 12 years old. For girls, respective baseline cutoff scores on Conners' ADHD/DSM-IV Scales - Teacher Version, for the same age groups were 16, 13 and 12

**Exclusion criteria**

1. Home-schooled children
2. Any medical condition that interfered with study assessments or that was not stable for ≥ 3 months before screening
3. Clinically significant abnormalities detected during screening
4. Family history of long-QT syndrome, current diagnosis or history of cardiac abnormalities, seizures, psychiatric disorders such as schizophrenia, schizoaffective disorder, severe obsessive-compulsive disorder, conduct disorder, autism, chronic tic disorder, Tourette's disorder or any mood or anxiety disorder
5. Antidepressants, antipsychotics, herbal preparations with psychotropic effects, amphetamine-based medications, benzodiazepines, barbiturates, sedatives or hypnotics, monoamine oxidase inhibitors and atomoxetine had to be stopped 1 to 4 weeks before randomisation according to their half-lives. All concomitant medications that could interfere with absorption, metabolism and distribution of study drug were excluded from the start of screening until the end of all evaluations. Over-the-counter analgesics, short-term antibiotic treatment for minor infections and any medication needed to treat adverse events were allowed
6. Additionally, patients who were judged by the investigator as likely to be non-compliant with study procedures, including those with a suspected history of substance abuse and those living with a person diagnosed with a substance abuse disorder, or whose parent or guardian was unable or unwilling to complete Conners' ADHD/DSM-IV Scales - Parent Version
7. Pregnancy or lactation
8. Positive drug screen

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| **Interventions** | Participants were randomly assigned to extended-release dexmethylphenidate hydrochloride or placebo<br>Fixed methylphenidate dosage: 10 mg, 20 mg or 30 mg<br>Administration schedule: once daily, morning<br>Duration of intervention: 5 weeks<br>Washout before study initiation: up to 28 days (duration dependent on the half-life of any previous psychotropic medication)<br>Titration period: 1 to 3 weeks, initiated after randomisation<br>Treatment compliance: 86% completed |
| **Outcomes** | **ADHD symptoms**<br>1. Conners' ADHD/DSM-IV - Teacher Version: rated by teacher at baseline and each week<br>2. Conners' ADHD/DSM-IV - Parent Version (including 12-item ADHD Index and 18-item DSM-IV Subscale total): rated by parent or guardian at baseline and each week<br>**Non-serious adverse events**<br>1. Regular monitoring and recording of adverse events, serious adverse events, vital signs, body weight, ECG, physical examination, haematology parameters, blood chemistry and urinalysis. While vital signs were recorded at every visit, physical, laboratory and ECG evaluations were completed during the screening visit and the final study visit. Weight was recorded at baseline and at the final visit. Notable value for weight loss was defined as a decrease from baseline weight at study end of 7% |
| **Notes** | Sample calculation: yes; 252 participants (63 per treatment group)<br>Ethics approval: Institutional review boards or ethical review committees at each centre approved the study<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Comment from study authors**<br>1. Limitations: short duration of study, forced-dose titration, not powered to assess differences in treatment effects within extended-release dexmethylphenidate hydrochloride groups<br>**Key conclusions of study authors**<br>1. All 3 doses of extended-release dexmethylphenidate hydrochloride (10 mg, 20 mg or 30 mg a day) were significantly more effective than placebo in improving ADHD symptoms, as confirmed by teacher, parent and clinician<br>2. Additionally, extended-release dexmethylphenidate hydrochloride was well tolerated and demonstrated a consistent safety profile. Mean changes from baseline in vital signs in extended-release dexmethylphenidate hydrochloride groups were small, clinically irrelevant, unrelated to dose and similar to placebo<br>3. Despite the forced-titration design of the study, the cardiovascular safety profile of extended-release dexmethylphenidate hydrochloride (10 mg/d, 20 mg/d and 30 mg/d) is similar to placebo in children with ADHD<br>**Comment from review authors**<br>1. Additionally, participants judged by the investigator as likely to be non-compliant with study procedures were excluded<br>Email correspondence with study authors in December 2013. We have contacted study authors twice in an attempt to obtain supplemental information regarding blinding, allocation concealment and weight loss. We have not received a response |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomisation was performed by using a validated system that automated the assignment of treatment arms to randomisation numbers in the specified ratio |
| Allocation concealment (selection bias) | Low risk | Allocation concealed |
| Blinding of participants and personnel (performance bias) | Unclear risk | Double-blind, but no detailed description |
| Blinding of outcome assessment (detection bias) | Unclear risk | Double-blind, but no detailed description |
| Incomplete outcome data (attrition bias) | Low risk | ITT population. LOCF<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Low risk | No |
| Vested interest bias | High risk | This study was funded by Novartis Pharmaceuticals Corporation. Novartis Pharma has been helping with development of the manuscript<br>Conflicts of interest: Several study authors have received research support from, are speakers for, are consultants of, are on the Advisory Board, have served on the Speakers' Bureaus of or are employees of several pharmaceutical companies |

*Chronis 2003*

| Methods | Eight-week within-participant, placebo-controlled, randomised, cross-over trial (Summer Treatment Camp (STP) with 3 interventions)<br>1. Methylphenidate<br>2. Adderall<br>3. Placebo<br>Phases: 2-week baseline assessment followed by 6-week medication trial |
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| Participants | Number of participants screened: 48<br>Number of participants included: 21 (19 boys, 2 girls). Participants were randomly assigned to 1 of 7 drug condition orders<br>Number of participants followed up: not stated<br>Number of withdrawals: not stated<br>Diagnosis of ADHD: DSM-IV (subtype not stated)<br>Age: mean 10.26 years (±1.9, range 6 to 12)<br>IQ: mean 109.9 (±18.8)<br>Methylphenidate naive: 14 children had received methylphenidate before start of the study<br>Ethnicity: White (100%)<br>Country: USA<br>Setting: out-patient clinic (summer treatment programme)<br>Comorbidity: learning problems (42.9%), oppositional defiant disorder (66.7%), conduct disorder (23.8%)<br>Comedication: not stated<br>Sociodemographics (median family income = $35,000/y (< $15,000/y to > $100,000/y); 66.7% of parents married<br>**Inclusion criterion**<br>1. DSM-IV diagnosis of ADHD<br>**Exclusion criteria**<br>1. None stated |
| Interventions | Participants were randomly assigned to 1 of 7 possible drug condition orders of immediate-release methylphenidate, Adderall and placebo<br>1. Placebo at 7:30 AM, 11: 30 AM and 3:30 PM<br>2. 0.3 mg/kg methylphenidate at 7:30 AM, 11:30 AM and 3:30 PM<br>3. 0.3 mg/kg methylphenidate at 7:30 AM and 11:30 AM with 0.15 mg/kg at 3:30 PM<br>4. 0.3 mg/kg methylphenidate at 7:30 AM only<br>5. 0.3 mg/kg Adderall at 7:30 AM and at 3:30 PM<br>6. 0.3 mg/kg Adderall at 7:30 AM with 0.15 mg/kg received at 3:30 PM<br>7. 0.3 mg/kg Adderall at 7:30 AM only<br>Mean methylphenidate dosage: not stated<br>Administration schedule: methylphenidate once, twice or 3 times daily according to the randomisation procedure<br>Duration of each medication condition: All participants received medication each Monday through Friday throughout a period of 6 weeks for a 24-day clinical assessment period. Assessment period was divided into three 8-day segments. Within each segment, placebo occurred twice and each other condition occurred once, with the order of conditions randomly assigned on a daily basis<br>Washout before study initiation: not stated<br>Medication-free period between interventions: none<br>Titration period: none<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. IOWA Conners' Rating Scale: rated by counsellors at the end of each day, by teachers after the classroom period each day and by parents in the evening<br>**Non-serious adverse events**<br>1. Pittsburgh Side Effects Rating Scale: rated by counsellors and teachers daily, rated by parents each evening with the addition of an item assessing difficulty falling asleep |

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| **Notes** | Sample calculation: no<br>Ethics approval: yes<br>Any withdrawals due to adverse events: none during the trial<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Comments from study authors**<br>1. Additional (late-afternoon) stimulant dose has beneficial effects on parent-child interactions<br>2. At the end of the Summer Treatment Programme (STP) for the 21 children, it was determined that 5 children did not show a sufficient positive response<br>**Key conclusions of study authors**<br>1. Single morning dose of Adderall had effects for an entire school day<br>2. Single dose of Adderall was equivalent to immediate-release methylphenidate twice/day<br>**Comments from review authors**<br>1. No mean methylphenidate dose<br>2. Behavioural intervention was also implemented during the entire 8-week study period<br>3. As intervention sequences were switched on a daily basis according to randomisation, we did not ask about first period data from this study<br>Email correspondence with study authors: July 2014. Emailed study authors twice to request additional information. Study author was not able to provide us with additional data |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | “Randomized by day”, no description of how randomisation took place |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Low risk | To ensure blinding, placebo capsules were given at 11:30 AM in the Adderall conditions and for applicable doses in the other conditions. Active medication and placebo were disguised in opaque gelation capsules by a local pharmacy and were dispensed in daily pill reminders by the study doctor. Furthermore, children were informed that they would be receiving 2 different kinds of medication to see how well they worked, and that some days they would receive inactive pills, but that they, their counsellors or teachers and their parents would not know what kind of pill they would get each day |
| Blinding of outcome assessment (detection bias) | Low risk | Children were informed that they would be receiving 2 different kinds of medication to see how well they worked, and that some days they would receive inactive pills, but that they, their counsellors or teachers and their parents would not know what kind of pill they would get each day |
| Incomplete outcome data (attrition bias) | Unclear risk | No mention of drop-out<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Low risk | All outcomes reported |
| Vested interest bias | High risk | Supported by a grant from Shire-Richwood Pharmaceuticals, Incorporated - manufacturer of Adderall - and from the National Institute of Mental Health (NIMH) |

*Coghill 2007*

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| **Methods** | Twelve-week randomised, placebo-controlled, double-blind cross-over trial with 3 interventions<br>1. Methylphenidate 0.3 mg/kg<br>2. Methylphenidate 0.6 mg/kg<br>3. Placebo |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 75 (all boys). Participants were randomly assigned to 1 of 6 possible drug condition orders<br>Number of participants followed up: not stated<br>Number of withdrawals: not stated<br>Diagnosis of ADHD: DSM-IV (combined type); ICD-10 (hyperkinetic disorder)<br>Age: mean not reported (range 7 to 15 years)<br>IQ: > 80<br>Methylphenidate naive: 100%<br>Ethnicity: not stated<br>Country: United Kingdom<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder (41.3%), conduct disorder (28%), depressive disorder (4%), generalised anxiety disorder (2.7%), separation anxiety disorder (4%), tic disorder (2.7%), social phobia (1.3%)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Eligible boys (scoring 1.5 SD from the mean on both Conners' Parent Rating Scale, Short Version, and Conners' Teacher Rating Scale, Short Version) were interviewed by an experienced child and adolescent psychiatrist using the Kiddie-Schedule for Affective Disorders and Schizophrenia Present and Lifetime<br>2. Those meeting criteria for hyperkinetic disorder (HD F 90) (ICD-10) and combined subtype (DSM-IV) were invited to participate<br>**Exclusion criteria**<br>1. History of neurological impairment/learning disability<br>2. IQ < 80<br>3. Chronic physical illness<br>4. Sensory or motor impairment<br>5. Current or previous exposure to stimulant medication<br>6. Abuse of any illegal drugs |
| **Interventions** | Participants were randomly assigned to 1 of 6 possible drug condition orders: 3 mg/kg/dose methylphenidate or 6 mg/kg/dose methylphenidate and placebo<br>Administration schedule: twice daily<br>Duration of each medication condition: 4 weeks<br>Washout before study initiation: no<br>Titration period: none<br>Treatment compliance: assessed by pill count and clinical enquiry but not further described |
| **Outcomes** | **ADHD symptoms**<br>1. Conners' Global Index, Parent Version and Teacher Version (10 item): rated by parents and teachers, each after 4 weeks |

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| **Notes** | Sample calculation: no<br>Ethics approval: yes<br>**Key conclusions of study authors**<br>1. Chronic methylphenidate predominantly enhanced neuropsychological functioning on "recognition memory" component tasks with modest "executive" demands<br>2. Neuropsychological measures offer only modest contributions to the prediction of clinical responses to methylphenidate in ADHD<br>**Comment from study authors**<br>1. Doses (0.3 mg/kg and 0.6 mg/kg) were chosen to reflect low- and high-dose regimens, respectively<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors in 2013. Emailed study authors twice with a request for additional information regarding protocol and number of participants on which analyses were based. Have not received a reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Participants were randomly assigned by an independent clinical trials pharmacist (using a computer-generated random number sequence with block design to ensure equal numbers in each treatment arm) |
| Allocation concealment (selection bias) | Low risk | Participants were randomly assigned by an independent clinical trials pharmacist |
| Blinding of participants and personnel (performance bias) | Unclear risk | Placebo-controlled, double-blind, no further information |
| Blinding of outcome assessment (detection bias) | Low risk | Clinical status was assessed by interview conducted by an experienced, blinded child and adolescent psychiatrist. Double-blind |
| Incomplete outcome data (attrition bias) | High risk | No description about how many participants were included in analyses |
| Selective reporting (reporting bias) | Unclear risk | No protocol identified |
| Vested interest bias | Unclear risk | This work was supported by a local trust through a Tenovus Scotland initiative<br>Conflicts of interest: Some study authors have affiliations with different pharmaceutical companies |

### *Coghill 2013*

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| **Methods** | Seven-week, multi-centre, double-blind, parallel, dose-optimised trial with 3 arms<br>1. Lisdexamfetamine dimesylate<br>2. OROS methylphenidate<br>3. Placebo |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 221 (181 boys, 40 girls)<br>Number of participants randomly assigned: methylphenidate 112, placebo 111<br>Number of participants followed up: methylphenidate 74, placebo 42<br>Number of withdrawals: methylphenidate 38, placebo 68<br>Diagnosis of ADHD: DSM-IV-TR (combined (methylphenidate 86.4%, placebo 79.1%), hyperactive-impulsive (methylphenidate 0.9%, placebo 6.4%), inattentive |

(methylphenidate 12.7%, placebo 14.5%)

Age: mean 10.9 years (range 6 to 17)

IQ: normal

Methylphenidate naive: methylphenidate 60 (54.1%), placebo 58 (52.7%)

Ethnicity: Caucasian (methylphenidate 96.4%, placebo 98.2%), African American (0%), Asian (0%), Hispanic/Latino (methylphenidate 1.8%, placebo 0%)

Countries: Germany, Sweden, Spain, Hungary, France, the UK, Italy, Belgium, Poland, the Netherlands

Setting: out-patient clinic

Comorbidity: oppositional defiant disorder (methylphenidate 9.0%, placebo 7.3%), concomitant psychiatric diagnosis (methylphenidate 26.1%, placebo 18.2%)

Comedication: not stated

Sociodemographics: not stated. No significant differences in baseline demographics were noted between the 2 groups

**Inclusion criteria**

1. Any sex
2. 6 to 17 years of age
3. Meeting criteria for ADHD according to DSM-IV-TR
4. Baseline ADHD moderate severity with ADHD-RS-IV score of 28 or higher
5. Age-appropriate intellectual functioning
6. Blood pressure measurements within the 95th percentile for age, sex and height
7. Ability to swallow a capsule
8. Girls of childbearing potential had to have a negative urine pregnancy test at baseline and to comply with any contraceptive requirements of the protocol

**Exclusion criteria**

1. Failure to respond to previous OROS methylphenidate therapy
2. Presence of a conduct disorder (excluding oppositional defiant disorder)
3. Pregnancy or lactation
4. Weight below 22.7 kg; body mass index (BMI, $kg/m^2$) > 97th percentile for age and sex
5. Positive urine drug test (with the exception of patient's current ADHD therapy)
6. Clinically significant electrocardiogram or laboratory abnormalities
7. Suspected substance abuse or dependence disorder (excluding nicotine) within the previous 6 months
8. History of seizures
9. Tics or Tourette's disorder
10. Known structural cardiac abnormality
11. Any other condition that might increase vulnerability to the sympathomimetic effects of a stimulant drug
12. Patients whose current ADHD medication provided effective control of symptoms with acceptable tolerability
13. Patient currently considered a suicide risk, with previous suicide attempt or with history of, or currently demonstrating, active suicidal ideation
14. Patient with glaucoma
15. Patient with documented allergy, hypersensitivity or intolerance to amphetamine or methylphenidate
16. Patient with documented allergy, hypersensitivity or intolerance to any excipients in test or reference products
17. Patients with known family history of sudden cardiac death or ventricular arrhythmia
18. Patients with pre-existing severe gastrointestinal tract narrowing (pathological or iatrogenic)
19. Patients unable to tolerate the study drug were withdrawn from the study

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| Interventions | Participants were randomly assigned to OROS methylphenidate or placebo<br>Mean methylphenidate dosage: 45.4 ± 12.7 mg/d (9.9% 18 mg, 19.8% 36 mg, 53.2% 54 mg)<br>Administration schedule: once a day, 7:00 AM<br>Duration of intervention: 7 weeks<br>Titration period: 4-week stepwise dose-optimisation period after randomisation. Three-week dose-maintenance period followed by 1-week washout and safety follow-up<br>Treatment compliance: 2 discontinued in placebo group because of non-compliance, 3 in methylphenidate group |
| Outcomes | **ADHD symptoms**<br>1. ADHD Rating Scale, Fourth Edition: total score at endpoint, investigator-rated at baseline and weekly for 7 weeks. Endpoint was defined as the last on-therapy, post-randomisation treatment visit with a valid ADHD Rating Scale, Fourth Edition, total score<br>**Quality of life**<br>1. Health Utilities Index-2: parent-rated at baseline and at weeks 4 and 7. Scoring ranges from 0.00 (dead) to 1.00 (perfect health). Higher scores represent better health status<br>2. Child Health and Illness Profile, Child Edition: Parent Report Form: parent-rated at baseline and at weeks 4 and 7. Questionnaire comprises 76 items classed into 5 domains and 12 associated subdomains. Most items relate to the past 4 weeks; the remainder are not associated with a specific time period. Parents use a 5-point response format to assess each item. Achievement is considered the primary health-related quality of life outcome<br>**Non-serious adverse events**<br>1. Safety assessments included treatment-emergent adverse events, clinical laboratory evaluations, physical examinations, vital signs and ECGs, observer-rated weekly for 8 weeks |

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| Notes | Sample calculation: yes<br><br>Ethics approval: approved by an independent ethics committee/institutional review board and regulatory agency at each centre (as appropriate) before study initiation<br><br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes<br><br>**Comments from study authors**<br><br>1. Individuals with comorbid conditions, such as post-traumatic stress disorder, bipolar affective disorder or severe anxiety disorder, were excluded from this study<br>2. As a result of European regulations, the maximum dose of OROS methylphenidate administered in this study was 54 mg/d. However, it is possible that the smaller than usual placebo response did, at least in part, contribute to this large treatment effect. ADHD is currently less frequently diagnosed in Europe than in North America, with evidence of underrecognition and underdiagnosis ( healthcareimprovementscotland.org). Consequently, it is likely that individuals who are diagnosed are at the more severe end of the spectrum and therefore would be less likely to show a response to placebo. Consistent with this suggestion, reassessment of data from the Multimodal Treatment of ADHD (MTA) study revealed that children who had been diagnosed with ADHD on the basis of DSM-IV criteria, but also met the more restrictive International Classification of Diseases 10th Revision criteria for hyperkinetic disorder, showed a more robust response to medication compared with those who met DSM-IV criteria alone<br><br>**Key conclusions of study authors**<br><br>1. In this European 7-week phase III study, lisdexamfetamine dimesylate was more effective than placebo in improving symptoms in children and adolescents with ADHD<br>2. Compared with placebo, significant improvements in both ADHD core symptoms and global functioning were observed<br>3. Lisdexamfetamine dimesylate was well tolerated, with treatment-emergent adverse effects consistent with those reported in previous studies<br>4. Robust efficacy outcomes were also observed for OROS methylphenidate, which was included in this study as a reference arm<br><br>**Comment from review authors**<br><br>1. Very confused on the number of participants included in the different analyses |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Interactive voice/web response system was used to allocate a unique randomisation number to each participant. Randomisation was stratified by country and age group (6 to 12 or 13 to 17 years of age) |
| Allocation concealment (selection bias) | Low risk | Interactive voice/web response system |
| Blinding of participants and personnel (performance bias) | Low risk | Study drugs were overencapsulated and appeared identical |
| Blinding of outcome assessment (detection bias) | Low risk | Masking: double-blinded (participant, caregiver, investigator, outcomes assessor) |
| Incomplete outcome data (attrition bias) | Unclear risk | LOCF approach was used when efficacy assessments were incomplete for a participant owing to early withdrawal from the study or for missing data. However, as the review authors cannot understand the relationship between the *n* of the full analysis set and the endpoint data, risk of bias was assessed as unclear<br>Selection bias (e.g. titration before randomisation → exclusion): none |
| Selective reporting (reporting bias) | Low risk | Outcomes according to protocol |
| Vested interest bias | High risk | Funded by Shire Development LLC<br>Conflicts of interest: C. Anderson, R. Civil, N. Higgins, A. Lyne and L. Squires are employees of Shire and own stock/stock options. Some study authors have received compensation for serving as consultants or speakers, or they or the institutions they work for have received research support or royalties from different companies or organisations |

*Connor 2000*

| Methods | Three-month, randomised, blind, parallel-group study with 3 arms<br>1. Methylphenidate and clonidine<br>2. Clonidine monotherapy<br>3. Methylphenidate monotherapy |
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| Participants | Number of participants screened: 24<br>Number of participants included: 24 (methylphenidate + clonidine 8 boys, 0 girls; placebo + clonidine 8 boys, 0 girls)<br>Number of participants randomly assigned: methylphenidate + clonidine 8, placebo + clonidine 8, placebo + methylphenidate 8<br>Number of participants followed up: methylphenidate + clonidine 8, placebo + clonidine 6<br>Number of withdrawals: methylphenidate + clonidine 0, placebo + clonidine 2<br>Diagnosis of ADHD: DSM-III-R (combined (100%))<br>Mean age: methylphenidate + clonidine 10.1 years, placebo + clonidine 9.3 years (range 6 to 16)<br>IQ: > 70<br>Methylphenidate naive: 54%<br>Ethnicity: Caucasian (11%), African American (1%), Asian (0%), Hispanic (0%), other (0%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder or conduct disorder (100%)<br>Comedication: not reported<br>Sociodemographics: No significant differences in baseline demographics were noted between groups<br>**Inclusion criteria**<br>1. DSM-III-R for ADHD<br>2. DSM-III-R for oppositional defiant disorder or conduct disorder, score of 1.5 SD above the mean for age and sex on the Parent Child Behavior Checklist, Attention problems scale (T score > 65) and a score on the Teacher Child Attention Problem Rating Scale of ≥ 93rd percentile<br>3. Score 1.5 SD above the mean for age and sex on the Parent or Teacher Child Behavior Checklist, Delinquency or Aggression problems scale<br>4. Normal findings from general physical examination by family physician within 6 months before study entry<br>**Exclusion criterion**<br>1. Medical history that contraindicated use of stimulants or clonidine |
| Interventions | Participants were randomly assigned to methylphenidate + clonidine or placebo + clonidine<br>Methylphenidate dose: 35.0 (5.67) mg/d<br>Administration schedule: b.i.d.<br>Duration of intervention: 12 weeks<br>Titration period: 4 weeks after randomisation<br>Treatment compliance: “All subjects were acceptably compliant with the protocol” |
| Outcomes | **General behaviour**<br>1. Disruptive Behavior Disorders Rating Scale: parent- and teacher-rated monthly<br>2. Home Situations Questionnaire: parent-rated monthly<br>3. School Situations Questionnaire: teacher-rated monthly<br>**Non-serious adverse events**<br>1. Possible side effects of methylphenidate and clonidine: Combined Stimulant/Clonidine Side Effects Rating Scale, parent- and teacher-rated monthly<br>2. Pulse and blood pressure obtained monthly. ECG measured after first month. Height and weight obtained monthly |

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| **Notes** | Intervention group: methylphenidate + clonidine; control group: placebo + clonidine<br>Ethics approval: yes<br>Sample calculation: no<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: June 2013. We obtained additional information from study authors, but it was not possible to receive supplemental data. We could not perform a meta-analysis on any of the outcomes, as we did not have relevant data and transformation was not possible |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | High risk | Eight participants were randomly assigned to each group. Three participants were previous methylphenidate treatment failures and refused randomisation to the methylphenidate-alone study arm. These 3 participants were partially randomly assigned to methylphenidate and clonidine or to clonidine alone. All other children were fully randomly assigned |
| Allocation concealment (selection bias) | Low risk | After study completion, the medication blind was broken. All medication capsules and placebo capsules were prepared by the UMMS (University of Massachusetts Medical School) Pharmacy in identical capsules to disguise taste and smell. All participants in all study groups received an equal number of capsules per day |
| Blinding of participants and personnel (performance bias) | Low risk | All teachers, school nurses, parents, children and research assistants completing dependent measures were blinded to the child's treatment group for the study duration. Completion of electrocardiograms (ECGs) for only 2 clonidine treatment groups may have broken blinding for parent raters and for the child (but not for teacher raters nor for research assistants administering the GDS, who remained blinded as to whether the child had received an ECG). This is not relevant to us, as we are using data only on the 2 groups completing ECGs |
| Blinding of outcome assessment (detection bias) | Low risk | As stated above |
| Incomplete outcome data (attrition bias) | Low risk | LOCF<br>Selection bias: no |
| Selective reporting (reporting bias) | Low risk | Reply from study author on our request for the protocol: protocol described in the study |
| Vested interest bias | Low risk | Supported by a UMMS (University of Massachusetts Medical School) Small Grants Project Award<br>Conflicts of interest: not stated |

*Cook 1993*

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| **Methods** | Six-week, double-blind, single cross-over, placebo-controlled study conducted on a group of 15 participants with ADD and a comparison group of 10 age-matched participants who did not have ADD<br>ADD group was randomly assigned to 1 of 2 experimental groups<br>1. Methylphenidate<br>2. Placebo |

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| Participants | **Regarding the ADD group**<br>Number of participants screened: not stated<br>Number of participants included: 15. Participants were randomly assigned to 1 of 2 possible drug condition orders<br>Number of participants followed up: 15<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-III (100% met DSM-III criteria for ADD with hyperactivity)<br>Age: mean 104.5 months (range 6 to 10 years)<br>IQ: mean 110.5 (SD 7.15)<br>Methylphenidate naive: 100%<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: central auditory processing disorder (80%)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Male<br>2. 6 to 10 years of age<br>3. IQ > 85<br>4. Clinical diagnosis of ADD from paediatrician and met DSM-III criteria for ADD on both Parent and Teacher Versions of the Swanson, Nolan and Pelham Scale; scored ≥ 15 points on the Parent Version of the Abbreviated Conners' Rating Scale<br>**Exclusion criteria**<br>Participants were excluded if they had<br>1. Seizures<br>2. Cerebral palsy<br>3. Learning disabilities<br>4. Speech or language problems<br>5. Vision or peripheral hearing problems<br>6. Thought disorder<br>7. Abnormal auditory brainstem evoked potentials<br>8. Previous drug treatment for ADD |
| Interventions | Participants were randomly assigned to 1 of 2 possible drug condition orders of methylphenidate and placebo<br>Mean methylphenidate dosage: 0.30 mg/kg (0.057)<br>Administration schedule: not stated<br>Duration of each medication condition: 3 weeks<br>Washout before study initiation: not relevant, 100% treatment naive<br>Medication-free period between interventions: minimum of 48 hours between the 2 interventions<br>Titration period: Dose was titrated up to a maximum (methylphenidate tablets or placebo tablets) over the first 3 weeks of the experimental period<br>Treatment compliance: not stated |

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| Outcomes | **ADHD symptoms**<br>1. Swanson, Nolan and Pelham Scale: teacher- and parent-rated, only items on the Inattention and Impulsivity subdomains, measured at the end of each treatment condition<br>2. ADD/H Comprehensive Teacher Rating Scale: measured at the end of each treatment condition<br>3. Abbreviated Conners' Rating Scale: parent-rated, measured at the end of each treatment condition |
| Notes | Sample calculation: no information<br>Ethics approval: yes<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Comment from study authors**<br>1. Limitations: The conclusion should not be generalised to results obtained with measures other than the 3 behaviour rating scales. The sample is small. Stimulant treatment periods were brief, and results may not have been maintained at the same level if the study had been conducted over a longer period<br>**Comment from review authors**<br>1. Read relevant parts of Dr. Cook's Ph.D. dissertation to get additional information about the study<br>**Key conclusion of study authors**<br>1. The implications of these results are 3-fold. First, sustained attention is a critical feature of performance on tests of central auditory processing disorder, and current diagnostic criteria for central auditory processing disorder make clinical separation of the 2 disorders problematic. Second, stimulants appear to be a useful treatment for symptoms of both ADD and central auditory processing disorder. Third, tests of central auditory processing disorder may provide a useful measure of ADD symptoms and response to stimulants<br>Email correspondence with study authors: September 2013. Emailed study author requesting additional information about the study and data. Dr. Cook referred to his Ph.D. dissertation, which we managed to get |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Participants were assigned to groups by a table of random numbers known only to the pharmacist |
| Allocation concealment (selection bias) | Low risk | Drugs were coded and administered by a pharmacist, and clinical titration of dosage was done by the participant's paediatrician; neither practitioner was involved in data collection |
| Blinding of participants and personnel (performance bias) | Low risk | Physician, audiologist, teachers and parents involved in behaviour ratings and participants themselves were blinded to assigned treatment |
| Blinding of outcome assessment (detection bias) | Low risk | Physician, audiologist, teachers and parents involved in behaviour ratings and participants themselves were blinded to assigned treatment |
| Incomplete outcome data (attrition bias) | Low risk | No incomplete outcome data<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Low risk | No |
| Vested interest bias | Low risk | Supported by the Medical Center Rehabilitation Hospital Foundation and the School of Medicine, University North Dakota; the Veterans Hospital; the Dakota Clinic; and The Neuropsychiatric Institute, Fargo, North Dakota<br>Conflicts of interest: not stated |

*Corkum 2008*

| Methods | Three-week, blind medication trial with cross-over design, in which children were randomly assigned to the following<br>1. Two different doses of methylphenidate (low and moderate)<br>2. Placebo |
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| Participants | Number of participants recruited: 28<br>Number of participants included: 21 (15 boys, 6 girls)<br>Number of withdrawals: 7 children excluded from final data analyses<br>Diagnosis of ADHD: DSM-IV (combined type (52%), hyperactive-impulsive type (10%), inattentive type (38%))<br>Age: mean not reported (range 6 years 1 month to 12 years 1 month)<br>IQ: no intellectual disability<br>Methylphenidate naive: All participants were stimulant medication-naive<br>Comorbidity: learning disabilities (29%), oppositional defiant disorder (10%), conduct disorder (0%), generalised anxiety disorder (0%), depression (0%)<br>Setting: out-patient clinic<br>Country: Canada<br>Ethnicity: All participants were Caucasian<br>Sociodemographics: predominantly middle-class families<br>**Inclusion criteria**<br>1. Stimulant medication-naive<br>2. DSM-IV criteria for 1 of the 3 ADHD subtypes<br>3. Received a recommendation to initiate a trial of methylphenidate following assessment<br>4. Parents/caregivers agreed to initiate a stimulant medication trial through the clinic paediatrician<br>**Exclusion criteria**<br>1. IQ < 1 SD below the mean on the Wechsler Intelligence Scale for Children, Fourth Edition<br>2. Known neurological, metabolic or seizure disorder<br>3. Currently taking other psychotropic medications or medications for sleep disturbances<br>4. Symptoms of an intrinsic sleep disorder (i.e. sleep apnoea, restless legs syndrome or periodic limb movements in sleep) or a sleep-onset disorder based on parent report<br>5. Reached criteria for another mental health disorder that was considered<br>6. Primary to the ADHD diagnosis (e.g. autism) |
| Interventions | Participants were randomly assigned to 1 of 3 medication-dosing schedules, including 1 week of baseline, placebo and low and moderate immediate-release methylphenidate (ritalin) dose condition. Children weighing ≤ 25 kg received 5-mg and 10-mg doses; children weighing > 25 kg received 10-mg and 15-mg doses. Children received medication<br>t.i.d. (8:00 AM, 12:00 PM, 4:00 PM)<br>Treatment compliance: no information |
| Outcomes | **ADHD symptoms**<br>1. Conners' Parent and Teacher Rating Scale - Revised, Short Form: rated weekly<br>**Non-serious adverse events**<br>1. Sleep Disturbances Scale for Children based on child's sleep over previous week: rated by parents<br>2. Actigraphy<br>3. Sleep diary |

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| **Notes** | Sample calculation: not stated<br>Ethics approval: yes<br>**Key conclusion of study authors**<br>1. Based on findings from the current study, we would encourage physicians and parents to closely monitor children's sleep when treating ADHD with stimulant medication, and to carefully weigh the benefits of improved behavioural functioning while taking medication against the potential negative consequences of sleep<br>**Comment from review authors**<br>1. Paper includes data on adverse effects: sleep disturbance (actigraph data, sleep diary data, Sleep Disturbances Scale for Children data) related to methylphenidate treatment compared with placebo<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: no<br>Email correspondence with study authors: August to October 2013. We received supplemental information regarding additional data from study authors, but we never received first period data from the cross-over trial |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Baseline data from 1 week were collected, followed by a 3-week medication trial with random assignment of children to 1 of 3 medication-dosing schedules. The original, fully randomised schedule was modified after a pilot study, conducted before the current study, indicated that children receiving a moderate dose before the low dose of methylphenidate reported increased side effects and were more likely to stop taking the third dose (4:00 PM) of medication |
| Allocation concealment (selection bias) | Low risk | Pharmacy local to the ADHD clinic prepared both placebo and active medication, which were packaged into identical gelatin capsules |
| Blinding of participants and personnel (performance bias) | Low risk | Child, family, school personnel and study investigators were unaware of the randomisation schedule. This information was made available only to the paediatrician and the pharmacist |
| Blinding of outcome assessment (detection bias) | Low risk | Child, family, school personnel and study investigators were unaware of the randomisation schedule. This information was made available only to the paediatrician and the pharmacist |
| Incomplete outcome data (attrition bias) | Unclear risk | 7 children excluded from final data analyses for the following reasons: actigraphic problems (i.e. data failure/loss of actigraph/refusal to wear actigraph) (n = 5), withdrawal of consent due to marital discord (n = 1) and decision to try alternative medication immediately before the start of the medication trial (n = 1) |
| Selective reporting (reporting bias) | Low risk | No subsequent correspondence with first study author regarding additional information on reporting |
| Vested interest bias | Low risk | Research was supported by a grant from the Izaak Walton Killam<br>IWK Health Centre in Halifax, Nova Scotia<br>Conflicts of interest: "none declared" |

*Cox 2006*

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| **Methods** | Randomised, double-blind, placebo-controlled, cross-over trial of adolescent drivers with ADHD who were assessed on a driving simulator after taking<br>1. 72 mg of OROS methylphenidate<br>2. 30 mg of extended-release mixed amphetamine salts<br>3. Placebo<br>Phases: 3 (2 relevant phases) |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 35 (19 boys, 16 girls). Participants were randomly assigned to 1 of 2 relevant (n = 3) possible drug condition orders<br>Number of participants followed up: 35<br>Number of withdrawals: 2<br>Diagnosis of ADHD: DSM-IV (combined 21 (60%), hyperactive-impulsive 2 (6%), inattentive 12 (34%))<br>Age: mean 17.8 years (range 16 to 19)<br>IQ: not stated<br>Methylphenidate naive: not stated<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: agoraphobia (2.9%), conduct disorder and marijuana abuse (2.9%), obsessive-compulsive disorder (2.9%), obsessive-compulsive disorder and hypomania (2.9%), nicotine dependence (5.7%)<br>Comedication: 2 were taking no medication, 21 were taking methylphenidate and 12 were taking amphetamine formulations at the start of the study<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Adolescent drivers<br>2. 16 to 19 years of age<br>3. ADHD according to DSM-IV. To meet inclusion criteria for a diagnosis of ADHD, adolescents first needed to surpass clinical cutoffs for ADHD on a commonly used parent rating scale, the ADHD Rating Scale, Fourth Edition<br>4. Psychiatrist confirmed ADHD diagnosis with the Standardized Interview for Adult ADHD (DSM-IV)<br>5. Positive history of stimulant responsiveness, as disclosed by adolescents and by parent reports; current licence to drive and reported daily driving activity<br>**Exclusion criteria**<br>1. Adolescents were excluded when they had a history of tics or any adverse reaction to stimulant medication<br>2. History of substance abuse disclosed by patient or parent<br>3. Co-existing medical condition or medication usage known to interfere with safe administration of stimulant medications |

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| Interventions | Participants were randomly assigned to 1 of 2 relevant drug condition orders of methylphenidate and placebo<br>Mean methylphenidate dosage: 72 mg/d<br>Administration schedule: 2 overlaid capsules/tablets in blister packs each day on awakening<br>Duration of each medication condition: 17 days<br>Washout before study initiation: not stated<br>Medication-free period between interventions: 4 to 21 days between OROS methylphenidate and mixed amphetamine salts<br>Titration period: half dose (36 mg/d OROS methylphenidate) days 1 to 5, full dose (72 mg/d OROS methylphenidate) days 6 to 17 initiated after randomisation<br>Treatment compliance: not stated. Pill counts were completed at each study visit |
| Outcomes | **Non-serious adverse events**<br>1. Throughout the study, only 1 adverse event was reported - urinary difficulty. This adverse event occurred during treatment with 36 mg of OROS methylphenidate and was resolved after 2 days without discontinuation of the medicine<br>2. Self-Reported Stimulant Drug Side Effects Rating Scale on days 5 and 10 |
| Notes | Sample calculation: no<br>Ethics approval: yes<br>**Comments from study authors**<br>1. Automobile accidents are the leading cause of death among adolescents, and collisions are 2 to 4 times more likely to occur among adolescents with ADHD<br>2. Studies have demonstrated that stimulants improve driving performance<br>3. Results provide evidence supporting most literature on children with short-acting stimulants; longer-acting stimulants appear equally effective for female and male post-pubertal adolescents with ADHD<br>4. Limitation of this study is that few participants with hyperactive subtype were included, limiting extrapolation of results to this subgroup<br>**Key conclusions of study authors**<br>1. This study validates the use of stimulants to improve driving performance in adolescents with attention deficit hyperactivity disorder<br>2. In this study, OROS methylphenidate promoted significantly improved driving performance compared with placebo and extended-release mixed amphetamine salts<br>**Comments from review authors**<br>1. Effects of methylphenidate were also measured, but not in comparison with placebo. Therefore, we could not use these data in the review<br>2. Some participants are older than 18 years. However, as mean age is > 19 years, this study is still included but was tested by sensitivity analyses<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; excluded if any history of adverse events to stimulant medications<br>Email correspondence with study authors: February 2014. We received additional information from study authors. Data from the Self-Reported Stimulant Drug Side Effects Rating Scale are no longer available |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "Using a random-numbers table, each participant was assigned" |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Unclear risk | Treatments were provided in different forms: "Participants took 2 overlaid capsules/tablets in blister packs each day on awakening". Participants and research assistants were blinded to medication conditions |
| Blinding of outcome assessment (detection bias) | High risk | "Participants were either tested on placebo or were not required to come in for testing". Participants and research assistants were blinded to medication condition |
| Incomplete outcome data (attrition bias) | Low risk | Email correspondence with study author: no drop-outs and all were followed-up ( Krogh 2013b [pers comm] )<br>Selection bias (e.g. titration after randomisation → exclusion): none described |
| Selective reporting (reporting bias) | Low risk | Email correspondence with study author, who stated that all planned outcome measures and analyses are described in the papers ( Krogh 2013b [pers comm] ) |
| Vested interest bias | High risk | Study was supported by funding from McNeil Pediatrics, a division of McNeil-PPC Incorporated<br>Conflicts of interest: none described |

### *Douglas 1986*

| Methods | Five-day cross-over trial with 2 interventions<br>1. Methylphenidate (0.3 mg/kg capsules each dose, morning + afternoon)<br>2. Placebo (100 mg lactose capsules)<br>**Phases**<br>1. Screening session about a week before testing (given practice on all tasks in the test battery; appropriate level was established for each child on tasks graded for difficulty level)<br>2. Five days of testing. Children received drug (D) or placebo (P) according to 1 of 4 possible orders: (1) PDDPP: (2) DPPDD; (3) DDPPD; (4) PPDDP. Testings were received each morning according to 4 test orders: (1) ABCDEF; (2) ACBEDF; (3) ADEBCF and (4) AEDCBF<br>Before the study was undertaken, 16 drug and test order combinations for the morning test battery were ordered randomly. As participants entered the study, they were assigned to these drug-plus-test order combinations until all 16 participants had been assigned. The order of the 2 tests in the afternoon battery (arithmetic and word discovery) was alternated over children, and each child received tests in the same order over 5 days of testing |
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| Participants | Number of participants screened: not stated<br><br>Number of participants included: 16 (15 boys, 1 girl). Participants were randomly assigned to 1 of 2 possible drug condition orders<br><br>Number of participants followed up: 16<br><br>Number of withdrawals: 0<br><br>Diagnosis of ADHD: DSM-III (subtypes not stated)<br><br>Age: mean 9.2 years (range 6 to 11.6)<br><br>IQ: mean103.19 (range 89 to 125)<br><br>Methylphenidate naive: 13 (81%)<br><br>Ethnicity: not stated<br><br>Country: Canada<br><br>Setting: out-patient clinic<br><br>Comorbidity: not stated<br><br>Comedication: not stated<br><br>Sociodemographics: Children's families varied from I to V on the Hollingshead and Redlich Index (with most families falling within level III to IV (V being the poorest)<br><br>**Inclusion criteria**<br><br>1. Met criteria for a DSM-III diagnosis of ADHD (American Psychiatric Association, APA 1980)<br>2. Had to receive ratings above 1.5 (on a 0 to 3 scale) on the Hyperactivity Index of Revised Conners' Parent and Teacher Rating Scales<br><br>Participants were referred to the Hyperactivity Project at Montreal Children's Hospital by paediatricians or school personnel. Referral was based on presence of the following symptoms<br><br>1. Inattentiveness<br>2. Impulsivity<br>3. Hyperactivity<br>4. Restlessness<br>5. Poor compliance and poor self control<br><br>Symptoms were of sufficient severity to prompt referring physicians to consider a trial on stimulant medication<br><br>**Exclusion criteria**<br><br>1. Psychosis<br>2. Serious visual, auditory or language deficits<br>3. Diagnosed as brain damaged<br>4. Restless behaviour attributable to emotional problems or a stressful home environment<br>5. Appearance of symptoms before age five and evidence that symptoms were chronic and pervasive |

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| Interventions | Participants were randomly assigned to 1 of 4 possible orders of drug (D) or placebo (P): (1) PDDPP; (2) DPPDD; (3) DDPPD; (4) PPDDP. On days when participants were assigned to active medication, they received a capsule containing the quantity of medication closest to a calculated dose of 0.3 mg/kg for each dose (morning and afternoon)<br>Mean methylphenidate dosage: not stated<br>Administration schedule: morning capsule administered approximately 1 hour after breakfast and 45 minutes before morning test battery was administered. Second capsule, identical to the morning capsule, administered before child left for lunch and returned to school. Time between morning and afternoon capsule was approximately 3½ hours<br>Duration of each medication condition: 1 day each; in all 2 or 3 days, depending on order of drugs assigned<br>Washout before study initiation: 24 hours before screening, 48 hours before first testing day<br>Titration period: none<br>Treatment compliance: capsule administered by examiner |
| Outcomes | **ADHD symptoms**<br>1. Hyperactivity Index from Conners' Revised Teacher Rating Scale: examiner-rated, at end of each morning of individual testing<br>2. Hyperactivity Index from Conners' Revised Teacher Rating Scale: teacher-rated, each afternoon<br>Score for the Index is based on the mean of item ratings on a 4-point scale (0 to 3) |
| Notes | Sample calculation: no<br>Ethics approval: yes<br>**Key conclusions of study authors**<br>1. Results indicate methylphenidate-induced improvement in most measures<br>2. Drug-induced changes reflected increased output, accuracy and efficiency and improved learning acquisition. Evidence of increased effort and self correcting behaviours was found<br>3. It is argued that review authors have underestimated the potential of stimulants to improve performance of ADD-H children on academic, learning and cognitive tasks<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: none stated<br>Email correspondence with study authors: July 2014. Emailed study authors to ask for additional information. Received information on ethics approval, but first study author was not able to provide additional data or information on the study |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not stated |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Unclear risk | Not stated |
| Blinding of outcome assessment (detection bias) | High risk | Capsule was administered by examiner |
| Incomplete outcome data (attrition bias) | Unclear risk | In a few cases in which data were missing, scores from 1 or 2 days were used to compute means for drug and placebo conditions. No information on drop-out rate |
| Selective reporting (reporting bias) | Unclear risk | No protocol |
| Vested interest bias | Low risk | Research was supported by Grant Number MA 6913, from the Medical Research Council of Canada<br>Conflicts of interest: no information |

*Douglas 1995*

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| Methods | Eight-day, double-blind, cross-over trial in which participants were randomly assigned to different doses of methylphenidate and placebo<br>1. 0.3 mg/kg methylphenidate<br>2. 0.6 mg/kg methylphenidate<br>3. 0.9 mg/kg methylphenidate<br>4. Placebo<br>**Phases**<br>1. Assessment week 1: 4 different doses given on 4 different days<br>2. Assessment week 2: same structure as assessment week 1 |

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| Participants | Number of participants screened: not stated<br>Number of participants included: 17 (16 boys, 1 girl). Participants were randomly assigned to 1 of 24 possible drug condition orders<br>Number of participants followed up: not stated<br>Number of withdrawals: not stated<br>Diagnosis of ADHD: DSM-III-R. Also had to meet DSM-III criteria for ADD with hyperactivity<br>Age: mean 9 years 5 months (range 6 years 3 months to 11 years 9 months)<br>IQ: mean 104.3 (range 89.0 to 127)<br>Methylphenidate naive: 53%<br>Ethnicity: not stated<br>Country: Canada<br>Setting: treatment centre (hospital) or out-patient clinic<br>Comorbidity: oppositional defiant disorder (71%), conduct disorder (18%)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. DMS-III-R criteria for ADHD<br>2. DSM-III criteria for attention deficit disorder with hyperactivity<br>3. Ratings from both mothers and teachers at or above a criterion score of 1.5 on the Hyperactivity Index of the Revised Conners' Rating Scale<br>**Exclusion criteria**<br>1. IQ < 85<br>2. Serious visual, auditory or speech deficits<br>3. Evidence of organic damage<br>4. Evidence suggesting that symptoms could be attributed to emotional problems or a stressful home environment |
| Interventions | Participants were randomly assigned to 1 of 24 possible drug condition orders of methylphenidate (0.3 mg/kg, 0.6 mg/kg, 0.9 mg/kg) and placebo<br>Mean methylphenidate dosage: 0.3 mg/kg: 9.71; 0.6 mg/kg: 19.42; 0.9 mg/kg: 29.14<br>Administration schedule: once daily<br>Duration of each medication condition: 1 day; each child received each dosage twice during the study (i.e. during first and second assessment weeks)<br>Washout before study initiation: In the case of children currently receiving stimulants, medication was discontinued ≥ 48 hours before screening<br>Titration period: none<br>Treatment compliance: To ensure compliance, medications were administered at the laboratory |
| Outcomes | **Non-serious adverse events**<br>1. Not described as a measure for the trial, but the Barkley Side Effects Rating Scale is mentioned |

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| **Notes** | Sample calculation: no information<br>Ethics approval: no information.<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Key conclusion of study authors**<br>1. Under acute dosage conditions as used in this study, methylphenidate doses up to 0.9 mg/kg had an increasingly positive effect on measures of mental flexibility and other cognitive processes<br>Email correspondence with study authors: October 2013. Emailed last study author twice to get supplemental information (protocol, ethics approval, data on side effects, etc.) but received no response. Therefore we included no data from this study |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Drug order was determined by consecutive assignment to a randomly ordered list of 24 possible combinations of 4 medication levels for each of the 2 testing weeks |
| Allocation concealment (selection bias) | Low risk | Drug order was determined by consecutive assignment to a randomly ordered list of 24 possible combinations of 4 medication levels for each of the 2 testing weeks. To maximise blindness of examiners, all participants received a different drug order for assessment weeks 1 and 2 |
| Blinding of participants and personnel (performance bias) | Low risk | Medications containing active drug and placebo were prepared in identical opaque gelatin capsules and were administered in a double-blind fashion |
| Blinding of outcome assessment (detection bias) | Low risk | To maximise blindness of examiners, all participants received a different drug order during assessment weeks 1 and 2 |
| Incomplete outcome data (attrition bias) | Unclear risk | Not stated whether any participants were LTFU |
| Selective reporting (reporting bias) | Unclear risk | No information |
| Vested interest bias | Low risk | Funded by grants from the Medical Research Council of Canada and by William T. Grant Foundation Faculty Scholar Program<br>Conflicts of interest: none |

### *DuPaul 1996*

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| **Methods** | Four-week, double-blind, placebo-controlled, cross-over trial in which participants were randomly assigned to 3 doses of methylphenidate<br>1. 0.16 mg/kg<br>2. 0.29 mg/kg<br>3. 0.42mg/kg<br>4. Placebo |

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| Participants | Number of participants screened: not stated<br>Number of participants included: 24 (19 boys, 5 girls). Participants were randomly assigned to 1 of 6 possible drug condition orders<br>Number of participants followed up: 24<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-III-R (subtype not stated)<br>Age: mean 11.09 years (range 9 to 15)<br>IQ: > 70<br>Methylphenidate naive: not stated<br>Ethnicity: Caucasian (100%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder (21%), conduct disorder (% not reported)<br>Comedication: not stated<br>Sociodemographics: Children were primarily from lower middle class and middle class families<br>**Inclusion criteria**<br>1. Parent and/or teacher referral to an out-patient ADHD clinic due to reported problems with inattention, impulsivity and/or overactivity<br>2. Parent interview indicating that child met DSM-III-R (American Psychiatric Association, APA 1987) criteria for ADHD<br>3. Independent diagnosis of ADHD by psychologist and paediatrician using DSM-III-R criteria for ADHD<br>4. Parent or teacher ratings on the Attention problem scale of the Child Behavior Checklist (Achenbach 1991), resulting in a T score ≥ 65 (i.e. 1.5 SD above the mean)<br>5. ≥ 9 years old and able to read self report questionnaires independently<br>**Exclusion criteria**<br>1. Evidence of mental retardation, gross sensory or motor disabilities, seizure disorder, autism, psychosis, tic disorders or Tourette's syndrome, or significant cardiac problems<br>2. Currently receiving psychotropic medication |
| Interventions | Participants were randomly assigned to 1 of 6 possible drug condition orders of low- (0.16 mg/kg; SD 0.08), moderate- (0.29 mg/kg; SD 0.11 kg) and high-dose (0.42 mg/kg; SD 0.14) methylphenidate and placebo<br>Administration schedule: b.i.d., morning, noon<br>Duration of each medication condition: 1 week<br>Washout before study initiation: not stated<br>Titration period: none<br>Treatment compliance: No participant was removed from the investigation for non-compliance (e.g. > 1 day of failure to administer medication as scheduled) |
| Outcomes | **ADHD symptoms**<br>1. ADHD Rating Scale: teacher and parent ratings<br>**Non-serious adverse events**<br>1. Barkley Side Effects Rating Scale (17 items, 0 = absent, severity rated from 0 to 9): rated by participants at the end of each dosage condition |

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| **Notes** | Sample calculation: no information<br>Ethics approval: Human Subjects Research Board at the University of Massachusetts Medical Center<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Comments from study authors**<br>1. Conclusions based on present findings are limited by several factors<br>2. Among others, sample size may have diminished power to detect methylphenidate effects on key variables, especially analyses of side effect ratings<br>3. Also results are generalisable only to children with ADHD between 9 and 15 years of age<br>Email correspondence with study authors: January 2013 to August 2013. Emailed first study author regarding additional information. Not able to get all data requested, as study author no longer has these data |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Children were randomly assigned to 1 of 6 possible orders of methylphenidate dosage |
| Allocation concealment (selection bias) | Low risk | Medication was prepared by the hospital pharmacy in increments of 5 mg and packaged within opaque gelatin capsules |
| Blinding of participants and personnel (performance bias) | Low risk | Participants, their parents and teachers and the research assistant in charge of collecting data were blinded to the order of medication |
| Blinding of outcome assessment (detection bias) | Low risk | Participants, their parents and teachers and the research assistant in charge of collecting data were blinded to the order of medication |
| Incomplete outcome data (attrition bias) | Low risk | No<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Low risk | Analyses on all dependent measures in the study are reported in the article |
| Vested interest bias | Low risk | No conflicts of interest |

### *Duric 2012*

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| **Methods** | Randomised, controlled trial, parallel with 3 arms<br>1. Neurofeedback group<br>2. Methylphenidate group<br>3. Methylphenidate + neurofeedback group |

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| Participants | Number of participants screened: 628<br>Number of participants included: 130<br>Number of participants randomly assigned: methylphenidate 44, control 42<br>Number of participants followed up: methylphenidate 30 (23 boys, 7 girls), control 30 (22 boys, 8 girls)<br>Number of withdrawals: methylphenidate 14, control 12<br>Diagnosis of ADHD: ICD-10 (subtype not stated)<br>Age: methylphenidate 11.2 (SD 2.8), control 11.4 (SD 3.1)<br>IQ: mean 87<br>Methyphenidate-naive: not stated<br>Ethnicity: not stated<br>Country: Norway<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: No significant differences in baseline demographics were noted between the 2 groups<br>**Inclusion criteria**<br>1. ICD-10 criteria for diagnosis of ADHD<br>2. 6 to 18 years of age<br>3. IQ > 70<br>**Exclusion criteria**<br>1. None stated |
| Interventions | Participants were randomly assigned to methylphenidate and neurofeedback (intervention group) or to neurofeedback (control group)<br>Methylphenidate dosage: 20 mg daily to 60 mg daily. No placebo pill<br>Administration schedule: twice per day<br>Duration of intervention: 11 to 13 weeks<br>Titration period: not stated<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. Two core ADHD symptoms – attention and hyperactivity, Assessment of Disruptive Behavior Disorders Rating Scale for parents: rated at baseline and 1 week after neurofeedback had been completed (between weeks 11 and 13 after start of intervention) |
| Notes | Ethics approval: yes<br>**Comments from study authors**<br>1. Factors that may result in ADHD symptom improvement: extraordinary amount of time spent with therapist during neurofeedback, better motivation for change in ADHD symptoms and cognitive-behavioural training induced under neurofeedback<br>2. For Attention rating, methylphenidate + neurofeedback and methylphenidate, no significant differences were noted between pre-treatment and post-treatment values<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: March to June 2013. Emailed first study author. All questions were answered |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Children with ADHD were randomly placed into 3 groups |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | High risk | No blinding, as it is not a “pure” placebo group |
| Blinding of outcome assessment (detection bias) | High risk | No blinding of parents |
| Incomplete outcome data (attrition bias) | Low risk | No |
| Selective reporting (reporting bias) | Low risk | Outcomes reported according to protocol |
| Vested interest bias | Low risk | No<br>Conflicts of interest: Study authors declare no potential conflicts of interests with regard to authorship or publication of this article |

*Döpfner 2004*

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| Methods | Randomised, double-dummy, double-blind, cross-over, multi-centre trial with 3 interventions<br>1. Immediate-release methylphenidate 10 mg to 40 mg<br>2. Extended-release methylphenidate 10 mg to 40 mg<br>3. Placebo<br>Phases: Trial was subdivided into 5 stages: pre-screening, run-in phase (duration: 1 workday), trial phases 1 and 2 (duration in each case: 4 workdays plus weekend) and trial phase 3 (duration: 4 workdays). Participants also received a behavioural therapy intervention and social skills training at school |

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| Participants | Number of participants screened: not stated<br>Number of participants included: 82. Participants were randomly assigned to different orders of immediate-release methylphenidate, extended-release methylphenidate and placebo<br>Number of participants followed up: 79 (71 boys, 8 girls)<br>Number of withdrawals: 3<br>**Regarding the group followed up**<br>Diagnosis of ADHD: DSM-IV or ICD-10 (combined (92.4%), hyperactive-impulsive (0%), inattentive (7.6%))<br>Age: mean 10 years (range 6 to 16)<br>IQ: 103 ± 10.4<br>Methylphenidate naive: 0%<br>Ethnicity: not stated<br>Country: Germany<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder/conduct disorder (44%)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Meeting criteria for an ICD-10 diagnosis of Hyperkinetic disorder (F90) or for a DSM-IV diagnosis of ADHD<br>2. Between 8 and 15 years of age<br>3. Methylphenidate responders on the basis of clinical assessment and after careful titration<br>4. All patients had to be treated with immediate-release methylphenidate at least twice daily or once daily with a retard preparation<br>5. During previous month, methylphenidate dosage had to be unchanged. Daily methylphenidate dosage was ≥ 10 mg<br>6. IQ ≥ 85<br>7. Body weight > 20 kg<br>8. Written informed consent of parents and participants to join the trial<br>**Exclusion criteria**<br>1. Patients attending schools for mentally handicapped, sensory handicapped or physically handicapped children<br>2. Patients who, during the past 4 weeks, were treated with other medication because of ADHD, apart from methylphenidate<br>3. Diagnosis of a severe developmental disorder or psychosis<br>4. Previous convulsive disorder; EEG indicated susceptibility to convulsions<br>5. Case history of pathological changes in liver function or liver disease<br>6. Severe depressive disorder (Child Behavior Checklist, teacher-rated, > 70 on the Anxiety-depression scale) or a severe anxiety disorder according to clinical diagnosis |

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| Interventions | Participants were randomly assigned<br>Mean methylphenidate dosage: 22 mg ± 6 mg. Dosage was identical in methylphenidate groups but did not exceed 1 mg/kg body weight. Thus, 9 (11%) participants received a daily dose of 10 mg, 54 (68%) received 20 mg, 14 (17%) received 30 mg and 2 (3 %) received 40 mg.<br>Administration schedule: 9:00 AM and 1:00 PM<br>Duration of each medication condition: 4 days, and for trial phase 1 + 2 (also weekends)<br>Washout before study initiation: none<br>Medication-free period between interventions: none<br>Titration period: had to be oriented to the optimum individual dosage previously determined in clinical treatment trials initiated before randomisation<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. Swanson, Kotkit, Agler, M-Flynn and Pelham Scale: rated by clinic personnel/caregiver staff for each child at 9:00 AM, 11:00 AM, 12:30 PM, 3:00 PM and 4.15 PM<br>2. Fremdbeurteilungsbogen für Hyperkinetische Störungen: staff/personnel-rated, at 1:00 PM and 4:45 PM<br>**Non-serious adverse events**<br>1. Questionnaire on side effects (Side Effects Rating Scale) |

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| Notes | Sample calculation: not stated<br><br>Ethics approval: approved by local university ethics committees<br><br>**Comment from study authors**<br><br>1. Althogh the analogue classroom attempts to mimic many aspects of a regular school classroom, it represents a unique setting that may influence behaviour. Analogue assessments included only ADHD participants; no control or normal participants were available for comparison<br><br>Carry-over effect: As no evidence for possible carry-over effects was noted, no secondary analyses for carry-over effects were performed<br><br>**Key conclusions of study authors**<br><br>1. These data provide support for the benefit of this novel, once-daily methylphenidate preparation for the treatment of ADHD<br>2. On all measures analysed, both b.i.d. immediate-release methylphenidate and extended-release methylphenidate produced significant improvement relative to placebo. Moreover, extended-release methylphenidate was not significantly different from b.i.d. immediate-release methylphenidate, even longer than 7 hours after dosing<br>3. Longer duration of action of Medikinet Retard has the potential to simplify psychostimulant treatment, thus reducing dose diversion and eliminating the need for in-school administration<br><br>**Comments from review authors**<br><br>1. For the article in German (Döpfner 2003 in Döpfner 2004), only 1 review author who knew German extracted the data. All other articles have been assessed for data by 2 review authors. We received Döpfner 2003 from HB Pharma<br>2. Eighteen participants in the sample from Clinic for Neuropediatrics, University of Kiel, received response cost token-based behaviour training (RCT) (Gerber 2012 in Döpfner 2004)<br><br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate: yes; included only methylphenidate responders<br><br>Email correspondence with study authors. We received some data from study authors in July 2013. We sent 2 additional emails to different study authors to request data in July 2014 but received no answer |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Order in which participants were allocated to respective treatment arms was randomly assigned |
| Allocation concealment (selection bias) | Unclear risk | Order in which participants were allocated to respective treatment arms was randomly assigned |
| Blinding of participants and personnel (performance bias) | Low risk | To guarantee a double-blind trial, the double-dummy method was used (i.e. participants took the capsule once a day and the tablets twice daily). Only 1 of the 2 galenical forms contained the active substance; the other form contained placebo. In the placebo group, participants took both placebo capsules and placebo tablets |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not stated |
| Incomplete outcome data (attrition bias) | Unclear risk | Not stated |
| Selective reporting (reporting bias) | Unclear risk | No protocol obtained |
| Vested interest bias | High risk | Study was conducted and sponsored by MEDICE Arzneimittel Pütter GmbH & Co. KG as part of the drug approval process for Medikinet-Retard™<br>Conflicts of interest: Some study authors have affiliations with medical companies |

### *Epstein 2011*

| Methods | Cross-over trial with 2 interventions<br>Three preliminary phases to determine optimal dose followed by 2-phase trial of the following<br>1. Optimal dose of methylphenidate<br>2. Placebo |
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| Participants | Number of participants screened: not stated<br>Number of participants included: not clear<br>Number of participants followed up: 93 (numbers of boys and girls: not stated)<br>Number of withdrawals: not clear<br>Diagnosis of ADHD: DSM-IV (combined (n = 45), hyperactive-impulsive (n = 48), inattentive (n = 0))<br>Age: mean 8.11 years (range 7 to 11)<br>IQ: mean 105.58<br>Methylphenidate naive: 100%<br>Ethnicity: Caucasian (75%), African American (22%), other (3%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder (n = 34), conduct disorder (n = 4), anxiety disorders (n = 31), mood disorders (n = 2)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criterion**<br>1. Children 7 to 11 years of age who met the diagnostic criteria for ADHD, plus 6 non-overlapping symptoms in a symptom domain on the Diagnostic Interview for Children - Parent Report and Vanderbilt Teacher Rating Scale; both parents and teachers reported ≥ 4 symptoms in that domain<br>**Exclusion criterion**<br>1. Children with an IQ below 80 (on the Wechsler Abbreviated Scale of Intelligence) or a score below 80 on the Reading or Numerical operations subtests of the Wechsler Individual Achievement Test or possible organic brain injury |
| Interventions | Participants were randomly assigned to an optimal dose of methylphenidate and placebo<br>Mean methylphenidate dosage: 1.13 mg/kg<br>Administration schedule: testing 1 to 4 hours after medication ingestion<br>Duration of each medication condition: 1 week<br>Washout before study initiation: no apparent washout<br>Titration period: Each of the 3 doses was trialled for 1 week before random assignment to identify an optimal dose<br>Treatment compliance: not reported |
| Outcomes | **ADHD symptoms**<br>1. Vanderbilt ADHD Rating Scale: completed by parents and teachers at the end of 1 week<br>**Non-serious adverse events**<br>1. Referred to the Pittsburgh Side Effects Rating Scale: completed by parents and teachers at the end of each week, but data were not reported |

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| **Notes** | Sample calculation: not stated<br>Ethics approval: not stated<br>Funding: National Institute of Health (NIH) and National Institute of Mental Health (NIMH)<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Comments from study authors**<br>1. Although we used a placebo-controlled, double-blind titration trial to determine optimal dosage, the highest dosage used in this trial was 54 mg for children ≧ 25 kg and 36 mg for children < 25 kg<br>2. Also, a significant minority of children (24%) exited the titration trial, with the placebo dosage as their optimal dosage, which is comparable with the stimulant response rate in other studies. The fact that 19% of children in the optimal dose condition received the same stimulant dosage (i.e. placebo) as was received by the placebo control group may have affected the ability of this study to detect between-group differences for some study outcomes (e.g. accuracy)<br>**Key conclusion of study authors**<br>1. None regarding our outcomes of interest<br>Email correspondence with study authors: April 2014. We were able to obtain supplemental information regarding data |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Blinding of participants and personnel (performance bias) | Low risk | "Double-blind"; capsules were "identical" (p 2, p 1063) |
| Blinding of outcome assessment (detection bias) | Low risk | "Double-blind", capsules were "identical" (p 2, p 1063) |
| Incomplete outcome data (attrition bias) | Unclear risk | Not clear whether any participants were LTFU |
| Selective reporting (reporting bias) | Low risk | No selective reporting |
| Vested interest bias | Low risk | No evidence of vested interests<br>No evidence of conflicts of interest |

### *Fabiano 2007*

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| **Methods** | Randomised, double-blind, within-participant design, cross-over trial with 2 interventions<br>1. Methylphenidate<br>2. Placebo<br>Phases: 0.15 mg/kg, 0.30 mg/kg and 0.60 mg/kg. Medication was randomly assigned for each child and varied daily during a 9-week summer treatment programme |

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| Participants | Number of participants screened: not stated<br>Number of participants included: 48 (44 boys, 4 girls). Participants were randomly assigned to 1 of 4 possible drug condition orders<br>Number of participants followed up: 47<br>Number of withdrawals: 1<br>Diagnosis of ADHD: DSM-IV (combined (not stated), hyperactive-impulsive (not stated), inattentive (not stated))<br>Age: mean 9.35 years (SD 1.98, range 5 to 12)<br>IQ: 106.33 (SD 14.61)<br>Methylphenidate naive: not stated<br>Ethnicity: Caucasian (79%); African American (12.5%); Hispanic, Native American or mixed race (8.5%)<br>Country: USA<br>Setting: out-patient clinic (summer treatment programme)<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* diagnostic criteria for ADHD<br>2. Estimated full-scale IQ ≥ 80<br>3. No documented adverse response or non-response to methylphenidate<br>4. No medical condition that would contraindicate use of methylphenidate<br>**Exclusion criteria**<br>1. None stated |
| Interventions | Participants were randomly assigned to 1 of 3 possible drug condition orders of immediate-release methylphenidate (0.15 mg/kg, 0.30 mg/kg and 0.60 mg/kg) and placebo<br>Mean methylphenidate dosage: 5.03 mg (range 2.5 to 10), 10.8 mg (range 5 to 20) and 21 mg (range 12.5 to 30)<br>Administration schedule: 3 times daily (7:45 AM, 11:45 PM and 3:45 PM)<br>Duration of each medication condition: varied daily<br>Washout before study initiation: none<br>Titration period: none/duration initiated before/after randomisation<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. IOWA Conners' Rating Scale (inattention-impulsivity-overactivity): teacher- and observer-rated, daily<br>**General behaviour**<br>1. IOWA Conners' Rating Scale (oppositional defiance): teacher- and observer-rated, daily<br>**Non-serious adverse events**<br>1. Pittsburgh Side Effects Rating Scale: teacher-rated daily<br>2. Clinically significant adverse events: observer-rated daily |

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| **Notes** | Sample calculation: no<br>Ethics approval: yes<br>**Comments from study authors**<br>1. "The study was conducted in an analogue classroom setting" (as opposed to a community classroom)<br>2. "The treatments used were of short duration"<br>3. "Observers and raters were blind to medication condition but not to behaviour modification conditions"<br>4. Ratings from the Pittsburgh Side Effects Rating Scale were averaged across days within drug condition (regardless of behaviour modification condition) for the 47 children. One participant's medication was discontinued because of parental concerns about side effects (mainly buccal-lingual movements) after 2 days of treatment, and 1 child's afternoon dose was reduced on 0.60 mg/kg days because of parent-reported anxiety and mood symptoms. No other children had side effects rated by the teacher at an average level of moderate or severe<br>**Comments of review authors**<br>1. This study of placebo versus methylphenidate was conducted during different conditions of behaviour modification. We should consider whether to use only data from the non-behaviour modification condition or data from all conditions<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes<br>Email correspondence with study authors: April 2014. We obtained supplemental information regarding risk of bias. No further information was received |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomisation and allocation concealment were completed with a random number generator by a researcher not involved in treatment |
| Allocation concealment (selection bias) | Low risk | Randomisation and allocation concealment were completed with a random number generator by a researcher not involved in treatment |
| Blinding of participants and personnel (performance bias) | Low risk | "Medication assessment procedure was double-blinded" (p 201) "children, their parents, and all clinical staff members were blinded to medication condition" (p 202)<br>Medication was prepared in opaque capsules by a pharmacist not otherwise involved in the study. It was administered to children by research staff who were not involved in administration of behavioural treatment nor in daily activities |
| Blinding of outcome assessment (detection bias) | Low risk | Observers and raters were blinded to medication conditions |
| Incomplete outcome data (attrition bias) | High risk | One child's parents elected to stop medication for the child after 2 days because of their concerns about possible side effects of the medication. This child was not included in the analyses |
| Selective reporting (reporting bias) | Low risk | No protocol/design was published. All pre-specified outcomes of interest have been reported |
| Vested interest bias | Low risk | This study was funded by the National Institute of Mental Health (NIMH) grant MH62946<br>Conflicts of interest: supported only by National Institutes |

*Findling 2006*

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| **Methods** | Three-week, randomised, double-blind, parallel trial with 3 arms<br>1. Immediate-release methylphenidate (Ritalin)<br>2. Modified-release methylphenidate (Equasym, EqXL)<br>3. Placebo |
| **Participants** | Number of participants screened: 346<br>Number of participants randomly assigned: 327<br>Number of participants included: 318; immediate-release methylphenidate 133, modified-release methylphenidate (EqXL) 139, placebo 46<br>Number of participants followed up: immediate-release methylphenidate 120, modified-release methylphenidate (EqXL) 120, placebo 39 (number in each arm is only per protocol population)<br>Number of withdrawals: not stated<br>Diagnosis of ADHD: DSM-IV (combined (71%), hyperactive-impulsive (6%), inattentive (23%))<br>Age: mean 9.5 years (range not reported)<br>IQ: above 80<br>Sex: 252 boys, 66 girls<br>Methylphenidate naive: 0%<br>Ethnicity: Caucasian (86%), African Caribbean (5.2%), Asian (0.3%), Hispanic (1.6%), other (6.9%)<br>Country: Australia, Canada, USA<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated. No significant differences in baseline demographics were noted between the 2 groups<br>**Inclusion criteria**<br>1. Male and female children<br>2. 6 to 12 years of age<br>3. Stable dose of methylphenidate 3 weeks before screening<br>4. Diagnosed with ADHD on the basis of DSM-IV criteria for any subtype and confirmed by administration of the Kiddie-Sads-Present and Lifetime Versions interview at screening<br>5. Attending a school setting in which a single teacher could make morning and afternoon assessments of the child's behaviour<br>**Exclusion criteria**<br>1. Female who had experienced menarche<br>2. Comorbid psychiatric disorder requiring medication<br>3. History of seizure or tic disorder or family history of Tourette's disorder<br>4. IQ test score below 80, or functioning at a level of intelligence indicative of an IQ below 80<br>5. Use of unapproved medication(s)<br>6. Use of an investigational product within 30 days before study entry<br>7. Concurrent chronic or acute illness, disability or medication that might confound the results of rating tests<br>8. Diagnosed with hyperthyroidism, glaucoma or eating disorder<br>9. Current substance abuse disorder or living with someone with a current substance abuse disorder<br>10. Demonstrated lack of response to methylphenidate |

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| Interventions | Participants were randomly assigned to immediate-release methylphenidate, extended-release methylphenidate or placebo<br><br>Mean methylphenidate dosage: not stated<br><br>Administration schedule: twice daily, morning and lunch<br><br>Duration of intervention: 3 weeks<br><br>Titration period: All participants were stable while taking methylphenidate medication before randomisation<br><br>Treatment compliance: not stated. Children with a previous total daily dose of 10 mg to 20 mg immediate-release methylphenidate or 20 mg extended-release methylphenidate were randomly assigned to receive 10 mg immediate-release methylphenidate twice daily, 20 mg modified-release methylphenidate (EqXL) once daily or placebo; children given a previous total daily dose of 25 mg to 40 mg immediate-release methylphenidate of > 20 mg to < 40 mg extended-release methylphenidate were randomly assigned to receive 20 mg immediate-release methylphenidate twice daily, 40 mg modified-release methylphenidate (EqXL) once daily or placebo; children given a previous total daily dose > 40 mg immediate-release methylphenidate or < 40 mg extended-release methylphenidate were randomly assigned to receive 20 mg immediate-release methylphenidate twice daily, 60 mg modified-release methylphenidate (EqXL) once daily or placebo |
| Outcomes | **ADHD symptoms**<br><br>1. Swanson, Nolan and Pelham, Fourth Edition: teacher-rated at baseline and weekly<br>2. Swanson, Nolan and Pelham, Fourth Edition: parent-rated at baseline and weekly, at the end of the child's day<br>3. IOWA Conners' Scale (Inattention-Impulsivity-Overactivity): teacher and parent<br><br>**General behaviour**<br><br>1. IOWA Conners' Rating Scale (oppositional defiance): teacher- and parent-rated, at baseline and weekly (2 hours post dose and 2 to 4 hours post lunch)<br><br>**Serious adverse events**<br><br>1. Only 1 serious adverse event (neutropenia) was reported during the study in EqXL treatment, but the investigator considered it unlikely to be related to the study medication<br><br>**Non-serious adverse events**<br><br>1. Barkley Side Effects Rating Scale: parent- and teacher-rated at baseline and weekly<br>2. Adverse events, laboratory parameters, vital signs, physical exam, observer-rated, time point not specified |
| Notes | Sample calculation: yes<br><br>Ethics approval: yes; independent ethics committee at each clinical site before study initiation<br><br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes<br><br>**Key conclusion of study authors**<br><br>1. Modified-release methylphenidate (EqXL) given once daily was non-inferior to immediate-release methylphenidate given twice daily. Both treatments were superior to placebo in reducing ADHD symptoms<br><br>**Comment from review authors**<br><br>1. September 2013. Not possible to contact study authors |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "Randomised" but did not state how |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | Both EqXL (modified-release methylphenidate) capsules and immediate-release methylphenidate tablets were overencapsulated in hard gelatin capsules identical to the placebo capsule |
| Blinding of outcome assessment (detection bias) | Unclear risk | No information |
| Incomplete outcome data (attrition bias) | High risk | Stated LOCF but primary efficacy population was the per protocol (PP) population, defined as participants who received study treatment and had ≥ 1 efficacy measurement after the first dose |
| Selective reporting (reporting bias) | Low risk | No protocol/design was published. All pre-specified outcomes of interest have been reported |
| Vested interest bias | High risk | Funding for this study was provided by Celltech Americas Incorporated, currently part of UCB (Union Chimique Belge)<br>Conflicts of interest: Drs. Hatch and DeCory and Miss Cameron were employees of Celltech at the time of this study. Dr. Findling received research support, acted as a consultant and/or served on a Speakers' Bureau for Abbott, AstraZeneca, Bristol-Myers Squibb, Celltech-Medeva, Forest, GlaxoSmithKline, Johnson & Johnson, Lilly, New River, Novartis, Otsuka, Pfizer, Sanofi-Synthelabo, Shire, Solvay and Wyeth. Dr. Quinn claims no competitive interests. Dr. McDowell has consulted for Janssen-Cilag and Lilly |

*Findling 2007*

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| Methods | Four-week, double-blind, randomised, placebo-controlled, cross-over trial with 4 interventions<br>Methylphenidate (at 3 different doses, in the morning and at midday)<br>1. 5 mg<br>2. 10 mg<br>3. 15 mg<br>4. Placebo<br>**Phases**<br>Participants were assigned to receive, at random, 1 of 6 possible dosing orders that included the following<br>1. Placebo, 5 mg, 10 mg, 15 mg<br>2. Placebo, 10 mg, 15 mg, 5 mg<br>3. 5 mg, placebo, 10 mg, 15 mg<br>4. 5 mg, 10 mg, 15 mg, placebo<br>5. 10 mg, 15 mg, placebo, 5 mg<br>6. 10 mg, 15 mg, 5 mg, placebo<br>Schedules were designed in such a way that participants did not receive the 15 mg dose before the 10 mg dose, so in the event that a participant experienced adverse events while taking a lower dose, the 15 mg dose was not administered |

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| Participants | Number of participants screened: not stated<br>Number of participants included: 20. Participants were randomly assigned to 1 of 6 possible drug condition orders<br>Number of participants followed up: 16 (12 boys, 4 girls)<br>Number of withdrawals: 4<br>**Demographic data regarding the 16 who completed the study**<br>Diagnosis of ADHD: DSM-IV (combined (94%), inattentive (6%))<br>Age: mean 10.43 years (range 5 to 17)<br>IQ: > 70<br>Methylphenidate naive: not stated<br>Ethnicity: White (75%), African American (6%), Hispanic (19%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: bipolar (100%), oppositional defiant disorder (50%), conduct disorder (25%), enuresis (12.5%), encopresis (12.5%)<br>Comedication: 100% divalproex sodium. Some received clonidine for sleep at night<br>Sociodemographics: not stated. No statistically significant differences in distribution based on sex, ethnicity, age group, rate/proportion of comorbid oppositional defiant disorder or comorbid conduct disorder were found between 6 six dosing order groups<br>**Inclusion criteria**<br>1. 5 to 17 years of age<br>2. Individuals meeting DSM-IV criteria for a diagnosis of bipolar spectrum disorder and a comorbid diagnosis of ADHD were eligible for study participation<br>3. Treated with fixed doses of mood stabilisers at the time of study enrolment for ≥ 5 days before receiving study medication<br>4. Eligible if study physician's clinical assessment indicated the need for a psychostimulant for treatment of "dysfunctional residual symptoms of ADHD"<br>**Exclusion criteria**<br>1. Mental retardation<br>2. Pervasive developmental disorder<br>3. Inability to swallow pills<br>4. History of alcohol or other substance abuse or dependence within 6 months before enrolment<br>5. Active neurological or other medical condition suspected to be related to mood symptoms<br>6. Pregnant females, those intending to become pregnant and sexually active female patients who were using an inadequate form of birth control were not permitted to participate<br>7. Participation required a negative qualitative pregnancy test within 2 weeks of receiving the first dose of double-blind treatment for female patients of childbearing potential<br>8. Significant symptoms of mania (Young Mania Rating Scale score > 13) or depression (CDRS-R > 40) during the week before enrolment and anticipated dosing changes for mood-stabilising agents<br>9. Individuals receiving a tricyclic antidepressant or antipsychotic agent and those with symptoms of psychosis or suicidal ideation<br>10. Females nursing an infant and patients experiencing significant medical or neurological illness were not permitted to participate |

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| Interventions | Participants were randomly assigned to 1 of 6 possible drug condition orders of methylphenidate (5 mg b.i.d., 10 mg b.i.d., 15 mg b.i.d.) and placebo<br>Mean methylphenidate dosage: not provided, as the trial compares methylphenidate at different doses<br>Administration schedule: morning and midday<br>Duration of each medication condition: 1 week<br>Washout before study initiation: not stated<br>Medication-free period between interventions: between lunchtime dose and morning dose the following day<br>Titration period: none. Dosing schedules were designed in such a way that patients did not receive the 15 mg dose before the 10 mg dose, so in the event that a participant experienced adverse events while on a lower dose, the 15 mg dose was not administered<br>Treatment compliance: One of 20 screened participants was withdrawn from the study because of poor compliance. Among the 16 who participated, no compliance issues were reported |
| Outcomes | **ADHD symptoms**<br>1. ADHD Rating Scale, Fourth Edition: rated weekly by parents<br>2. Conners' Parent Rating Scale (48-item): rated weekly<br>**General behaviour**<br>1. Conners' Parent Rating Scale, Conduct problem subscale<br>**Non-serious adverse events**<br>1. Child Depression Rating Scale - Revised: rated weekly<br>2. Young Mania Rating Scale: rated weekly.<br>3. Side Effects/Behavior Monitoring Scale: rated weekly at the study visit<br>4. Resting blood pressure and pulse recorded each week<br>5. Weight documented at baseline and at end of study |
| Notes | Sample calculation: yes<br>Ethics approval: yes<br>**Comments from study authors (limitations)**<br>1. Small sample size<br>2. Full consideration of dosing order effects was not possible because of the modest size of this study cohort<br>**Key conclusion of study authors**<br>1. Euthymic youths with bipolar disorder and ADHD may benefit from short-term concomitant treatment with methylphenidate<br>**Comment from review authors**<br>1. All participants have a bipolar disorder<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: yes; 2<br>Email correspondence with study authors: November 2013. We wrote to the study author twice to request a copy of the protocol and information about sample size and allocation concealment but have not received a response |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | A random numbers table was generated and was used by a pharmacist to assign dose orders to participants. Counterbalancing was applied in such a way that as each dose order was used, its number was eliminated from the next dose order assignment |
| Allocation concealment (selection bias) | Low risk | Placebo and methylphenidate in identical capsules. No participants were discontinued from this trial because of broken integrity of the blind |
| Blinding of participants and personnel (performance bias) | Low risk | At the conclusion of the 4-week study, study physician, participant and participant's guardian determined a "best dose week", taking into consideration behaviour ratings and reports of any adverse events. After all assessments had been completed, the study blind was broken to reveal the dose that had been prescribed during the previously identified 'best dose week'. No participants were discontinued from this trial because of broken integrity of the blind |
| Blinding of outcome assessment (detection bias) | Low risk | "After all of the assessments had been completed, the study blind was then broken to reveal the dose that had been prescribed during the previously identified 'best dose week'" |
| Incomplete outcome data (attrition bias) | Low risk | All data present |
| Selective reporting (reporting bias) | Unclear risk | No protocol identified |
| Vested interest bias | Unclear risk | Stanley Medical Research Institute<br>Conflicts of interest: Some study authors have affiliations with pharmaceutical companies |

### *Findling 2008*

| Methods | Seven-week randomised, phase III, double-blind, multi-centre, parallel-group, placebo-controlled, naturalistic home and school trial with 3 arms<br>1. Methylphenidate transdermal system patch + placebo capsule<br>2. OROS methylphenidate capsule + placebo patch<br>3. Placebo capsule + placebo patch<br>Five-week titration phase, 2-week maintenance phase |
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| Participants | Number of participants screened: not stated<br><br>Number of participants included: 282 (187 boys, 95 girls)<br><br>Number of participants randomly assigned (and administered ≥ 1 dose of study medication): methylphenidate transdermal system 100, OROS methylphenidate 94, placebo 88<br><br>Number of participants followed up: methylphenidate transdermal system 71, OROS methylphenidate 66, placebo 32<br><br>Number of withdrawals: methylphenidate transdermal system 27, OROS methylphenidate 25, placebo 53<br><br>Diagnosis of ADHD: DSM-IV-TR (combined (80.5%), hyperactive-impulsive (1.4%), inattentive (17.0%), unclassified (1.1%))<br><br>Age: mean 8.8 years (range 6 to 12). Methylphenidate transdermal system 8.9, OROS methylphenidate 8.8, placebo 8.5<br><br>IQ: ≥ 80<br><br>Methylphenidate naive: 86%<br><br>Ethnicity: Caucasian (77.3%), African American (14.5%), Asian (0.7%), Hispanic (not stated), other (7.4%)<br><br>Country: USA<br><br>Setting: out-patient clinic<br><br>Comorbidity: not stated<br><br>Comedication: not stated<br><br>Sociodemographics: not stated. No significant differences in baseline demographics (age, sex, ethnicity, ADHD subtype, prior ADHD medication use) among the 3 groups<br><br>**Inclusion criteria**<br><br>1. 6 to 12 years of age, inclusive<br>2. ADHD, DSM-IV-TR<br>3. Stimulant-naive or known to be stimulant-responsive<br>4. IQ ≥ 80<br>5. Total score of 26 on ADHD Rating Scale, Fourth Edition, while unmedicated<br>6. Normal laboratory parameters and vital signs, including ECG<br>7. Females of childbearing potential must have a negative serum beta human chorionic gonadotropin (HCG) pregnancy test at screening and a negative urine pregnancy test at baseline<br><br>**Exclusion criteria**<br><br>1. Comorbid psychiatric diagnosis (except oppositional defiant disorder)<br>2. History of seizures during the past 2 years<br>3. Tic disorder<br>4. Any concurrent illness or skin disorder that might compromise safety or study assessments<br>5. Ingestion of clonidine, atomoxetine, antidepressants, antihypertensives, investigational medications, hepatic or cytochrome (p 450) enzyme-altering agents, medications with central nervous system effects, sedatives, antipsychotics or anxiolytics within the 30 days before study entry<br>6. Overweight (body mass index (BMI)-for-age > 90th percentile) |

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| Interventions | Participants were randomly assigned to methylphenidate patch, OROS methylphenidate or placebo<br><br>Titration period: 5 weeks (after randomisation) of optimisation to 1 of 4 total daily dosage strength. OROS methylphenidate: 18 mg, 27 mg, 36 mg and 54 mg. Methylphenidate transdermal system and placebo transdermal system: 10 mg, 15 mg, 20 mg and 30 mg over a 9-hour period in patches of 12.5 cm², 18.75 cm² , 25 cm² and 37.5 cm², respectively<br><br>Administration schedule: Treatments were administered at approximately 7:00 AM each morning; patches were applied to the hip area and were worn for approximately 9 hours daily, different hip each day<br><br>Mean patch wear time: 8.70 (0.51) to 9.46 (0.53) hours<br><br>Duration of intervention: 7 weeks<br><br>Washout before study initiation: up to 28 days if applicable<br><br>Treatment compliance: mean compliance 97% to 99% during both study phases |
| Outcomes | **ADHD symptoms**<br><br>1. ADHD Rating Scale, Fourth Edition: clinician-rated, weekly<br>2. Conners' Teacher Rating Scale: teacher-rated, twice weekly<br>3. Conners' Parent Rating Scale: parent-rated, twice weekly<br><br>**Non-serious adverse events**<br><br>1. Evaluations for safety were performed at the end of each week during both dose-optimisation and dose-maintenance phases. Furthermore, adverse events were spontaneously reported as coded via MedDRA (7.0) Adverse Event Dictionary<br>2. Blood pressure, pulse, oral temperature, weight: weekly<br>3. Laboratory parameters: week 7<br>4. Sleep-related behaviours rated by parents each week using Children`s Sleep Habits Questionnaire<br>5. Skin reactions due to the patch investigated each week; Dermal Response Scale<br>6. ECG: final dose-optimisation visit and final study visit |

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| Notes | Sample calculation: yes (258 participants)<br><br>Ethics approval: yes<br><br>**Comments from study authors**<br><br>1. It is important to note, however, that effects reported are for baseline and endpoint reports of sleep problems; thus, these results may not generalise to the titration period. For example, sleep problems may have resulted in dosage adjustments and attenuation of sleep problems during titration<br>2. Respondents did not enter the maintenance phase if spontaneously reported side effects could not be controlled by adjusting the dose. Thus, participants with extreme insomnia would not have entered the maintenance phase<br>3. Rating scales for sleep problems may lack validity<br><br>**Key conclusions of study authors**<br><br>1. Results of this study suggest that the methylphenidate transdermal system is an efficacious treatment option for children with ADHD<br>2. Results of our analysis suggest that emergence or worsening of sleep problems in response to treatment of ADHD symptoms with OROS methylphenidate or methylphenidate transdermal system generally should not be a major concern to clinicians, children with ADHD or their parents after titration to an optimal dose, as described for this protocol. However, these suggestions should be considered in the light of other research that supports an effect of methylphenidate on insomnia and other sleep difficulties, especially when methylphenidate will be administered to children with pre-existing sleep difficulties. These findings should not be generalised to children who have not been titrated to an optimal dose<br><br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes. An inclusion criterion is that participants are stimulant-naive or stimulant-responsive<br><br>Any withdrawals due to adverse events: yes; 11<br><br>Email correspondence with study authors. June to September 2013. We attempted to obtain supplemental efficacy and safety data from study authors but without success |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
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| Random sequence generation (selection bias) | Low risk | Computer-generated random numbers schedule |
| Allocation concealment (selection bias) | Low risk | Computer-generated random numbers schedule |
| Blinding of participants and personnel (performance bias) | Low risk | Double-blind, double-dummy: Participants received both a patch and a capsule to be administered each day. Methylphenidate and placebo capsules were overencapsulated to blind the identity of the capsule's content |
| Blinding of outcome assessment (detection bias) | Unclear risk | Double-blind |
| Incomplete outcome data (attrition bias) | High risk | ITT, LOCF<br>Selection bias: yes; non-responders excluded during the study. Participants who did not reach an acceptable condition by the final dose-optimisation visit (week 5) were withdrawn from the study |
| Selective reporting (reporting bias) | Low risk | Outcomes reported according to protocol |
| Vested interest bias | High risk | This study was funded by Shire Development Incorporated, Wayne, Pennsylvania<br>Conflicts of interest: Some study authors received research support, acted as consultants and/or served on a Speakers' Bureau for several pharmaceutical companies |

*Findling 2010*

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| Methods | Phase IIIB, randomised, double-blind, parallel-group, placebo-controlled, multi-centre, dose-optimisation study evaluating the efficacy and safety of the following in adolescents 13 to 17 years of age with ADHD<br>1. Methylphenidate transdermal system (10-, 15-, 20- or 30-mg/9-hour patches)<br>2. Placebo transdermal system<br>Study consisted of 4 experimental periods<br>1. Screening and washout<br>2. Dose optimisation (5 weekly visits)<br>3. Dose maintenance (5 monthly visits)<br>4. Seven-day post-treatment follow-up<br>Follow-up consisted of an open-label extension study conducted to evaluate the safety and efficacy of the methylphenidate transdermal system (10-, 15-, 20- or 30-mg/9-hour patches) for participants who completed all required study visits; consisted of 3 experimental periods |
| Participants | By using 85% power to detect an effect size of 0.5 between active treatment and placebo at the significance level of 5%, it was estimated that 112 participants were needed for methylphenidate transdermal system groups and 56 for placebo transdermal system groups. Assuming a 20% drop-out rate, ~ 210 participants (methylphenidate transdermal system 140, placebo transdermal system 70) were required for the study<br>**For the double-blind, randomised, controlled trial**<br>Number of participants screened: not stated<br>Number of participants included: 217 (162 boys, 55 girls)<br>Number of participants randomly assigned: methylphenidate 145, placebo 72<br>Number of participants followed up (ITT population): methylphenidate 143, placebo 72<br>Number of withdrawals: methylphenidate 2, placebo 0<br>Number that completed 7-week dose-optimisation/dose-maintenance phase: |

methylphenidate 95, placebo 72

Diagnosis of ADHD: DSM-IV (types not stated)

Age: mean 14.6 years (SD 1.3, range 13 to 17)

IQ: ≥ 80

Methylphenidate naive: 122 (56%)

Ethnicity: Caucasian (77%), African American (18%), Asian (0.5%), other (4.5%)

Country: USA

Setting: out-patient clinic

Comorbidity: 0%

Comedication: not stated

Sociodemographics: not stated. No significant difference in baseline demographics were noted between the 2 groups

**For the open-label extension (regarding safety measures)**

Number of participants included: 163 (previously taking methylphenidate 110, placebo 53)

Number of participants followed up: 162 (121 boys, 41 girls)

Number of withdrawals: 1

Diagnosis of ADHD: DSM-IV (types not stated)

Age: 14.5 years (SD 1.24, range 13 to 17)

IQ: ≥ 80

Methylphenidate naive: 122 (56%)

Ethnicity: Caucasian (78%), African American (17%), Asian (0.6%), other (4.4%)

Country: USA

Comorbidity: 0 %

Comedication: not stated

Sociodemographics: not stated

**Inclusion criteria**

1. Male or female adolescents
2. 13 to 17 years of age
3. Primary diagnosis of ADHD according to DSM-IV
4. IQ score > 80
5. Total score ≥ 26 on the ADHD Rating Scale, Fourth Edition, at baseline
6. Participants were required to have ECG results within normal range or variants that were not clinically significant, as judged by investigators in conjunction with the central laboratory
7. Blood pressure measurements within the 95th percentile for age, sex and height
8. No current or past skin disease or other skin problems, including sensitive skin or signs of skin irritation
9. Females must have a negative urine pregnancy test at entry and must agree to use acceptable contraceptives throughout the study period and for 30 days the last dose of IP

Participant and parent of legally authorised representative (LAR) are able, willing and likely to fully comply with study procedures and restrictions

1. Regarding the 6-month open-label study: Participants must have completed all required study visits or a 5-week dose-optimisation period without achieving an acceptable condition (i.e. ≧ 25% decrease from baseline in a participant's ADHD Rating Scale, Fourth Edition, score with minimal side effects)

**Exclusion criteria**

1. Conduct disorder or comorbid psychiatric illness (such as clinically significant obsessive-compulsive disorder, depressive or anxiety disorder; post-traumatic stress disorder; psychosis; bipolar illness; or pervasive developmental disorder); history of structural cardiac abnormality, cardiomyopathy, cardiac rhythm abnormalities or other serious cardiac problems; suicidal ideation; alcohol or other substance abuse (except caffeine or nicotine) within the past 6 months

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| | 2. Seizures during the previous 2 years and a history of being non-responsive to psychostimulant treatment; use of clonidine, atomoxetine, antidepressants, sedatives, antipsychotics, anxiolytics, P450 enzyme-altering agents or other investigational medications within 30 days before screening<br>3. Female participant who is pregnant or lactating<br>**Regarding the 6-month open-label study**<br>1. Participants were not eligible to participate in the extension study if they were discontinued from the antecedent study because of a protocol violation (including non-compliance) or had experienced an adverse event for which continued treatment would be medically contraindicated, or a serious adverse event<br>2. Participants with considerable general medical illness (except mild, stable asthma) or an unstable medical condition, disability or other condition the investigator believed might interfere with or prevent completion of the study |
| Interventions | Participants were randomly assigned to methylphenidate transdermal (patches) or placebo<br>Mean methylphenidate dosage at week 7: 10 mg (4.2%), 15 mg (16.7%), 20 mg (24.0%), 30 mg (55.2%); median exposure time: 48 days (range 4 to 57)<br>Administration schedule: single patch in the morning, once daily for 9 hours<br>Duration of intervention: 7 weeks<br>Titration period: 5 weeks, initiated after randomisation<br>Treatment compliance: 124 fulfilled the protocol. However, it is not stated in the article how compliance regarding the medication had to be assessed to fulfil the protocol<br>Mean methylphenidate dosage at month 6: 10 mg (5.6%), 15 mg (7.9%), 20 mg (32.6%), 30 mg (53.9%); median exposure time: 168 days (range 3 to 200)<br>Administration schedule: single patch in the morning, once daily for 9 hours<br>Duration of intervention: 6 months<br>Titration period: 5 weeks of the 6 months<br>Treatment compliance: not stated. 88 fulfilled the protocol. However, it is not stated in the article how compliance regarding the medication had to be assessed to fulfil the protocol |

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| Outcomes | Regarding the 7-week parallel study<br>**ADHD symptoms**<br>1. ADHD Rating Scale, Clinicians: rated baseline and weekly for 7 weeks (each study visit)<br>2. Conners' Parent Rating Scale - Revised, Parents: rated baseline and weekly for 7 weeks (each study visit)<br>**Serious adverse events**<br>1. None<br>**Non-serious adverse events**<br>1. Adverse events monitored at each study visit. All AEs were coded using the MedDRA, Version 7.0<br>2. Height measurements were performed at screening and at the final double-blind study visit<br>3. Vital signs (systolic and diastolic blood pressure, pulse) and weight, at screening, at baseline and at each study visit<br>The investigator determined the clinical significance of any physical examination, height or vital sign measurement that was outside the normal range. Clinically significant deviations from measurements recorded at screening were reported as AEs. A 12-lead ECG evaluation was obtained at screening, at baseline, at week 5 and at the final double-blind study visit.Dermal skin reaction: Dermal Scale (DRS) was used to evaluate observed skin findings: range 0 to 7, where 0 shows no evidence of irritation<br>**Regarding 6-month open-label study**<br>1. Dose optimisation (5 weekly visits); dose maintenance (5 monthly visits)<br>a. AEs were monitored at each study visit and were assessed by an open-ended inquiry along with specific dermatological questions asked by an investigator or a qualified evaluator. AEs were considered treatment-emergent if they began or worsened on or after application of the first patch, and occurred before or at the same time as application of the patch. AEs coded and defined using the MedDRA, Version 7.03, at 7-day post-treatment follow-up<br>b. Height: measured at month 6 visit by the investigator<br>c. Weight: recorded at all visits (5) by the investigator<br>d. Vital signs (systolic blood pressure, diastolic blood pressure, pulse): measured at all study visits by the investigator. 12-Lead ECG performed at entry, week 4, month 3 and month 6 by the investigator<br>e. Blood and urine samples collected at entry, week 4, month 4 and month 6<br>f. Dermal skin reaction: measured by DRS at each study visit.<br>g. Sleep: measured by non-validated Post-Sleep Questionnaire. Measured at 6-month visit<br>Changes noted between evaluation data at study entry and data obtained at schedule visits deemed to be clinically significant by the investigator were considered an adverse event |

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| Notes | Sample calculation: yes<br><br>Ethics approval: yes<br><br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br><br>**Comments from study authors**<br><br>1. Given the short duration of this study, results do not characterise the long-term effects of treatment with methylphenidate transdermal system<br>2. It is important to note that participants who failed to respond to psychostimulants in the past and those with conduct disorder and other psychiatric comorbidity were excluded from the study<br>3. Regarding the 6-month study: no clinically significant findings between laboratory evaluation parameters obtained post entry relative to screening values obtained at the antecedent study<br>4. Limitations: This study used an open-label design; thus tolerability and effectiveness assessments are susceptible to observer bias. Another way in which results of long-term, open-label continuation studies may be biased is that participants who enrol in a study after participating in an antecedent trial may represent that subset of patients who have had improvement in ADHD symptoms and/or who did not experience substantial adverse events in the antecedent study<br><br>**Key conclusions of study authors**<br><br>1. Methylphenidate transdermal system therapy was generally well tolerated and resulted in significantly greater improvement in ADHD symptoms among adolescents when compared with the placebo transdermal system<br>2. Reported adverse events included those typically observed for oral methylphenidate, with the exception of generally mild application site erythema associated with transdermal delivery<br>3. Regarding the 6-month open-label study: Methylphenidate transdermal system was generally well tolerated, and adverse events were generally typical of those associated with oral methylphenidate, with the exception of application site reactions associated with transdermal delivery of methylphenidate<br><br>**Comments from review authors**<br><br>1. As already stated, people who earlier had failed to respond to psychostimulants were not included in the study. Therefore, results can be generalised only to responders<br>2. Risk of bias table done only for the 7-week parallel-group study<br>3. Regarding the 6-month open-label study: Participants who had not reached an acceptable response by the end of week 5 were withdrawn from the study |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Participants were allocated the next sequential randomisation number and received treatment that corresponded with that randomised number as given by an interactive voice response system |
| Allocation concealment (selection bias) | Low risk | Randomisation schedule was produced by computer software that incorporated a standard procedure for generating random numbers |
| Blinding of participants and personnel (performance bias) | Unclear risk | Double-blind, but no information on methylphenidate and placebo blinding |
| Blinding of outcome assessment (detection bias) | Unclear risk | Double-blind |
| Incomplete outcome data (attrition bias) | High risk | Efficacy analyses were performed on the ITT population, defined as all randomly assigned participants who received ≥ 1 dose of study medicine and ≥ 1 post-baseline primary efficacy assessment. Safety population was defined as all randomly assigned participants who received ≥ 1 dose of study medicine.<br>Selection bias (e.g. titration after randomisation → exclusion): yes. No further dose titration was permitted for any participant after week 5, and participants who had not reached an acceptable response by the end of week 5 were withdrawn from the study |
| Selective reporting (reporting bias) | Low risk | Protocol registered 12 July 2007. First participant consent was obtained 29 August 2007 for the open-label study |
| Vested interest bias | High risk | This study was funded by Shire Development Incorporated, which was involved in study design, conduct and data analysis. The open-label study was industry-sponsored<br>Conflicts of interest: Dr. Findling has acted as consultant to, has served on Speakers' Bureaus of and/or has received research support from Abbott, Addrenex, AstraZeneca, Biovail, Bristol-Myers Squibb, Eli Lilly, Forest Pharmaceuticals, GlaxoSmithKline, KemPharm, Johnson & Johnson, Lundbeck, Neuropharm, Novartis, Noven, Organon, Otsuka, Pfizer, sanofi-aventis, Sepracor, Shire, Solvay, Supernus, Validus and Wyeth. Dr. Turnbow receives or has received research support, acted as a consultant and/or served on Speakers' Bureaus for Eli Lilly, Novartis US, sanofi-aventis, Shire and UCB (Union Chimique Belge). Dr. Burnside has acted as consultant to, has served on Speakers' Bureaus of and/or has received research support from Eli Lilly, Johnson & Johnson, Shire and Wyeth. Dr. Melmed has acted as consultant to, has served on Speakers' Bureaus of and/or has received research support from Bristol-Myers, Eli Lilly, McNeil, Novartis and Shire. Drs. Civil and Li are full-time employees of Shire Development Incorporated |

*Fine 1993*

| Methods | Three-week double-blind, cross-over trial with 2 interventions<br>1. Methylphenidate b.i.d. (2 doses: 0.3 mg/kg and 0.6 mg/kg)<br>2. Placebo b.i.d.<br>Phases: medical trial or typical clinical procedure, concluded with recommendation for treatment, follow-up (6 weeks and 3 months) |
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| Participants | Number of participants screened: 24<br>Number of participants randomly assigned: 12 "typical clinical procedure", 12 "medical trial"<br>Number of participants included: 12 (sex not stated). Participants in the medical trial group were randomly assigned to different possible drug condition orders<br>Number of participants followed up: 12<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-III-R (subtype not stated)<br>Age: mean 101.58 months (range 6 to 10 years)<br>IQ: not stated<br>Methylphenidate naive: 12<br>Ethnicity: not stated<br>Country: Canada<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics (socioeconomic status calculated using Blishen Index; lower score indicates higher SES): medical trial: mean 3.42 (SD 0.90); typical clinical procedure: mean 3.50 (SD 1.88)<br>**Inclusion criterion**<br>1. ADHD diagnosis. Parent interview with psychiatrist, several parent (mother AND father) and teacher ratings. Included if any positive<br>**Exclusion criteria**<br>1. Physical or intellectual handicap<br>2. Tic disorders |
| Interventions | Participants in the medical trial group were randomly assigned to different possible drug condition orders of 0.3 mg/kg and 0.6 mg/kg methylphenidate and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: b.i.d.<br>Duration of each medication condition: "the different interventions were randomly assigned across days"<br>Washout before study initiation: not stated<br>Medication-free period between interventions: not stated<br>Titration period: not stated<br>Treatment compliance: missed pills mean 1.92 (SD 1.44). Furthermore, compliance was assessed by urine test. By 6-week follow-up, parent-reported compliance was 83%; by 3 months, it was 73% |
| Outcomes | **ADHD symptoms**<br>1. Abbreviated Conners' Rating Scale: rated on weekdays by teachers and on weekends by parents<br>2. Swanson, Nolan and Pelham: rated daily, but not stated by whom<br>**Non-serious adverse events**<br>1. Side effects questionnaire: rated weekly by parents ("Across the 12 children, ratings were available from an average of 2.58 placebo days, 1.33 low-dose MPH days and 1.75 high-dose MPH days") |

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| Notes | Sample calculation: not stated<br><br>Ethics approval: not stated<br><br>**Comments from study authors**<br><br>1. Small sample size<br>2. Rely on parent ratings to assess side effects<br><br>**Key conclusions of study authors**<br><br>1. Fine 1993: "Our analyses revealed that several side-effects appeared equally often on placebo as on active medication and the parents' reports of side effects are significantly related to reports of ADHD symptomatology" (p 28)<br>2. Johnston 1993 (in Fine 1993): "In summary, this study finds mixed support for the prediction that medication trials would enhance acceptability, satisfaction, and compliance associated with MPH" (p 728)<br><br>**Comments from review authors**<br><br>1. This trial aims to examine differences in attitudes of parents whose children participate in a medical trial or are subjected to "typical clinical procedure"<br>2. Only the medical trial group represents a cross-over design<br>3. Fine 1993 deals only with the medical trial group, and Johnston 1993 (in Fine 1993) deals with both<br><br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br><br>Any withdrawals due to adverse events: no<br><br>Email correspondence with study authors: June 2014. Emailed study authors for supplemental information and received the following response: "I did look at the questions, but unfortunately, given how long ago the study was conducted, I do not still have the data necessary to answer" (Krogh 2014b [pers comm] |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
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| Random sequence generation (selection bias) | Low risk | 24 children were matched in pairs on sex and age and then were randomly assigned to the medication trial or to the typical clinical procedure. Higher and lower doses of methylphenidate and placebo were randomly assigned across days by the hospital pharmacy |
| Allocation concealment (selection bias) | Low risk | Higher and lower doses of methylphenidate and placebo were randomly assigned across days by the hospital pharmacy. Active medication and placebo were packaged in capsule form to disguise taste and visual differences, and were dispensed in envelopes for daily use |
| Blinding of participants and personnel (performance bias) | Low risk | Parents, teacher, child and resident were blinded to the daily medication status of the child. "Active medication and placebo were packaged in capsule form to disguise taste and visual differences, and were dispensed in envelopes for daily use". All evaluations were conducted by psychiatric residents blinded to the hypotheses of the study |
| Blinding of outcome assessment (detection bias) | Low risk | Parents, teacher, child and resident were blinded to the daily medication status of the child. All evaluations were conducted by psychiatric residents blinded to the hypotheses of the study |
| Incomplete outcome data (attrition bias) | Unclear risk | Across 12 children, ratings were available for an average of 2.58 placebo days, 1.33 low-dose methylphenidate days and 1.75 high-dose methylphenidate days. Ratings for each child were averaged across each of the 3 treatment conditions. Data for all participants were available for measures of missed pills and appointments. One participant was missing on measures of parent-reported compliance at 6-week follow-up, and 2 participants at 3-month follow-up. Three participants lacked data for the number of missing envelopes. Four participants did not provide urine for analysis, and 4 were missing physician reports of compliance (6-week and 3-month follow-ups). As the result of intervening school holidays, teacher reports of compliance are available for only 16 children (8 in each condition) at each follow-up.<br>Methylphenidate non-responders were not excluded. Did not state the method used to account for missing outcome data |
| Selective reporting (reporting bias) | Unclear risk | All analyses mentioned are described, but no protocol was identified |
| Vested interest bias | High risk | Funding from CIBA-GEIGY Canada |

*Firestone 1981*

| Methods | Three-month, randomised, double-blind, placebo-controlled, parallel study, wherein participants were randomly assigned to 3 arms<br>1. Parent training + placebo (control group)<br>2. Parent training + methylphenidate (intervention group)<br>3. Methylphenidate |
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| Participants | Number of participants screened: 91<br>Number of participants included: not stated (includes boys and girls)<br>Number of participants randomly assigned: not stated<br>Number of participants followed up: intervention 18, control 13<br>Number of withdrawals: not stated<br>Diagnosis of ADHD: DSM-III<br>Age: mean 7.32 years (range 5 to 9)<br>Methylphenidate naive: not stated<br>Ethnicity: not stated<br>Country: not stated<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: not stated<br>IQ: 116<br>Sociodemographics: all children living at home with ≥ 1 parent. No significant differences in age and IQ between treatment groups. No data on remaining parameters<br>**Inclusion criteria**<br>1. 5 to 9 years of age<br>2. Fit DSM-III criteria for attention deficit disorder with hyperactivity, showing overactivity, short attention span, impulsivity, aggressiveness and oppositional behaviour, both at home and in school, since before 4 years of age<br>3. Hyperactivity Index of Conners' Behavior Rating Scale for teachers ≥ 15<br>4. IQ > 85<br>**Exclusion criteria**<br>1. Brain damage<br>2. Epilepsy<br>3. Psychosis |
| Interventions | Participants were randomly assigned to methylphenidate + parent training (intervention group) or to placebo + parent training (control group). First 3 to 4 weeks: Methylphenidate was titrated (after randomisation), starting with 5 mg b.i.d. (morning, noon), 7 days a week. After the titration period: Methylphenidate was given only on school days<br>Average methylphenidate dosage: 22 mg/d (range 10 mg/d to 30 mg/d)<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. Conners' Teacher Rating Scale 2, Conners' Parent Rating Scale subscale<br>2. Hyperactivity Index: rated by mothers post treatment |

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| **Notes** | Ethics approval: no information<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Key conclusions of study authors**<br>1. All groups showed improvement at home and in school; only with methylphenidate administration were gains in measures of attention and impulse control also seen<br>2. Results also revealed greater improvement in academic achievement and in classroom behaviour in medication groups as compared with placebo groups<br>3. No evidence showed significant benefit from the addition of parent training to administration of medication<br>**Comment from review authors**<br>1. First study author has retired; we were not able to get data from him (e.g. protocol, randomisation method) |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Children were randomly assigned; no description of how |
| Allocation concealment (selection bias) | Unclear risk | No data |
| Blinding of participants and personnel (performance bias) | Low risk | Parents, teachers, therapists and those testing the children were unaware of medication conditions |
| Blinding of outcome assessment (detection bias) | Low risk | Parents, teachers, therapists and those testing the children were unaware of medication conditions |
| Incomplete outcome data (attrition bias) | Unclear risk | No data<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): none |
| Selective reporting (reporting bias) | Unclear risk | No data |
| Vested interest bias | Low risk | Ministry of Health<br>Conflicts of interest: not stated |

### *Fitzpatrick 1992a*

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| **Methods** | Cross-over trial with 4 interventions<br>1. Sustained-release methylphenidate<br>2. Standard methylphenidate<br>3. Combination<br>4. Placebo<br>Phases: 4 pharmaceutical conditions, each lasting 2 weeks (including weekends), with different dosage schedules based on weight of child and type of intervention |

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| Participants | Number of participants screened: not stated<br>Number of participants included: 19 (17 boys, 2 girls). Participants were randomly assigned to 1 of 24 possible drug condition orders<br>Number of participants followed up: not stated<br>Number of withdrawals: not stated<br>Diagnosis of ADD: DSM-III during Diagnostic Instrument for Childhood and Adolescence (ADD with hyperactivity 16/19) (ADD without hyperactivity 3/19)<br>Age: mean 8.71 years (SD 1.33, range 6.9 to 11.5)<br>IQ: 114.11 (SD 13.34)<br>Methylphenidate naive: 18<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: oppositional disorder (n = 12), oppositional + conduct disorder (n = 1), enuresis (n = 2), encopresis (n = 2), phobia (n = 1), overanxious (n = 1), adjustment disorder (n = 1)<br>Comedication: not stated<br>Sociodemographics: middle class (Hollingshead 4-factor mean 38.11, SD 13.18)<br>**Inclusion criteria**<br>1. Not explicitly stated<br>**Exclusion criteria**<br>1. Not explicitly stated |
| Interventions | Participants were randomly assigned to 1 of 24 (3 methylphenidate and 1 placebo) possible drug condition orders of sustained-release methylphenidate (SR), standard methylphenidate (SA), methylphenidate combination and placebo<br>Mean methylphenidate dosage: SRSA-MPH 17.1 mg (0.56 mg/kg), SASR-MPH 20 mg (0.67 mg/kg), combination 11.8 mg SA MPH + 20 mg SR MPH (0.38 mg/kg SA, 0.67 mg/kg SR)<br>Administration schedule: sustained-release methylphenidate, mornings (8:00 AM) daily, SA MPH morning (8:00 AM) and noon daily<br>Duration of each medication condition: 2 weeks<br>Washout before study initiation: not stated<br>Medication-free period between interventions: not stated<br>Titration period: not stated<br>Treatment compliance: parents phoned weekly to encourage compliance. School nurse contacted at the beginning of each individual's participation to promote co-operation and to check on compliance |

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| Outcomes | **ADHD symptoms**<br>1. Conners' Hyperactivity Index: parent- and teacher-rated, weekly (although results were averaged over treatment phase)<br>2. IOWA Inattention/Overactivity and Aggression/Non-compliance Scales: parent- and teacher-rated, weekly<br>3. Hyperactivity, Attention and Aggression subscales of Loney's Time on Task Scale (TOTS): every 2 weeks<br>**General behaviour**<br>1. Selected items of Child Psychiatric Scale: observer, end of each laboratory session (i.e. after 14 days of treatment)<br>**Non-serious adverse events**<br>1. Interviewed: 12 side effect symptoms: drawn from Subject's Treatment Emergent Symptom Scale, parents, end of each treatment phase<br>2. Body weight: start of each laboratory session |
| Notes | Sample calculation: not stated<br>Ethics approval: not stated<br>**Key conclusions of study authors**<br>1. Methylphenidate conditions were superior to placebo and were comparable with one another<br>2. Findings suggest comparable effectiveness for sustained and standard preparations of methylphenidate<br>3. Improved behaviour and improved information processing under stimulant conditions<br>**Comment from review authors**<br>1. This study was not actually randomised; therefore we cannot use data on ADHD symptoms and general behaviour - only data on adverse events<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: not clear |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | High risk | Double-blind trial consisting of 4 pharmacological conditions, each lasting 2 weeks and ordered according to a Latin square (i.e. not randomly assigned) |
| Allocation concealment (selection bias) | High risk | Not randomised |
| Blinding of participants and personnel (performance bias) | Low risk | Double-blind. Blindness was maintained by administering placebo tablets consisting of the vehicle for the SA and SR preparations, respectively, as appropriate for each condition |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not stated |
| Incomplete outcome data (attrition bias) | Unclear risk | Data for 6 participants on Paired Associate Learning Test excluded, as they could not read well, but this was not 1 of our outcomes<br>Selection bias (e.g. titration after randomisation): no, but because of emergent side effects, reductions of 2.5 mg SA MPH per dose were performed blindly for 1 participant in the combined condition. Similarly, blinded (but sham) adjustments of SA placebo were made for 2 participants in the placebo phase and for 1 in the SR condition |
| Selective reporting (reporting bias) | Unclear risk | Not stated |
| Vested interest bias | Low risk | Research was supported by National Institute of Mental Health (NIMH) grant MH38118<br>Conflicts of interest: not stated |

### *Flapper 2008*

| Methods | Four-week, double-blind, randomised, placebo-controlled, cross-over study of methylphenidate and placebo with weekly switches of 4 dosage levels; capsules of<br>1. 0.5 mg/kg<br>2. 0.75 mg/kg<br>3. 1 mg/kg<br>4. Placebo<br>Methylphenidate-sensitive children continued in an open-label study for 4 weeks |
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| Participants | Number of participants screened: 80<br>Number of participants included: 30 (22 boys, 8 girls). Participants were randomly assigned to 1 of the possible drug orders of low-dose, moderate-dose and high-dose methylphenidate and placebo<br>Number of participants followed up: 30<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-IV (combined (37%), inattentive (57%), hyperactive-impulsive (7%))<br>Age: mean 105.2 months (SD 25.1, range 7 to 12 years)<br>IQ: > 70<br>Methylphenidate naive: 100%<br>Ethnicity: not stated<br>Country: the Netherlands<br>Setting: out-patient clinic<br>Comorbidity: developmental co-ordination disorder (100%)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. ADHD, DSM-IV<br>2. Developmental co-ordination disorder, DSM-IV<br>3. ADHD symptoms had to be severe for ≥ 6 items on the DSM-IV ADHD Rating Scale, Parent Version, investigator administered and scored<br>4. Total score on the Movement Assessment Battery for Children below the fifth centile<br>**Exclusion criteria**<br>1. Comorbid disorders (including pervasive developmental disorder)<br>2. Not medication-naive<br>3. IQ score below normal range (< 70), as assessed by the Wechsler Intelligence Scale for Children – Revised (Dutch Edition) |
| Interventions | Participants were randomly assigned to possible drug orders of the 3 daily doses of methylphenidate (0.5 mg/kg, 0.75 mg/kg, 1 mg/kg) and placebo<br>Mean optimal dosage: 0.66 mg/kg/d (SD 0.22)<br>Administration schedule: b.i.d.<br>Duration of each medication condition: 1 week<br>Washout before study initiation: none. All were medication naive<br>Medication-free period between interventions: none<br>Titration period: none<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. 18-Item ADHD Rating Scale, Fourth Edition: rated weekly (each Friday) by parents and teachers |

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| Notes | Sample calculation: yes<br><br>Ethics approval: Procedures were performed in accordance with the ethical standards of the University Medical Centre, University of Groningen<br><br>**Comment from study authors**<br><br>1. One aim of the study was to investigate the effectiveness of methylphenidate in improving the fine motor performance of children with ADHD and developmental co-ordination disorder (DCD). To prevent confounding by fluctuations in ADHD symptoms, these had to be reduced by selecting methylphenidate-sensitive children<br><br>**Key conclusions of study authors**<br><br>1. Children with ADHD/DCD and their parents rated overall quality of life as poorer than for healthy controls, manifested in domains of motor and autonomic functioning, as well as cognitive and psychosocial functioning<br>2. In our study, significant improvements in health-related quality of life were noted after treatment with methylphenidate, as was improvement in symptoms of ADHD and motor functioning<br>3. Fine motor performance in children with ADHD-DCD was poorer before use of methylphenidate than afterwards<br>4. Impairment in manual dexterity and poor quality of handwriting and drawing improved after methylphenidate use, but performance remained poorer than in the control group<br><br>**Comment from review authors**<br><br>1. Only data from the 4-week cross-over trial are useful for the review; therefore all data extracted were derived from the cross-over period<br><br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br><br>Any withdrawals due to adverse events: no<br><br>Email correspondence with study authors: August 2013 to January 2014. We obtained supplemental information regarding participant demographics and efficacy data |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random order by pharmacist |
| Allocation concealment (selection bias) | Low risk | Medication codes were broken at time 2 (endpoint) |
| Blinding of participants and personnel (performance bias) | Low risk | Parents, teachers, children and paediatrician were kept blinded to the child's drug condition and dosage level |
| Blinding of outcome assessment (detection bias) | Low risk | Parents, teachers, children and paediatrician were kept blinded to the child's drug condition and dosage level |
| Incomplete outcome data (attrition bias) | Low risk | No participant withdrew; no ITT was needed. Seven children whose ADHD symptoms were not sensitive enough to methylphenidate (effect < 25%) were excluded from the 4-week open-label period. However, as we are using in this review only data from the preceding cross-over period, exclusion of these children does not cause high risk of bias<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Low risk | No reporting bias |
| Vested interest bias | Low risk | For this study, no funding was available. This double-blind placebo-controlled (DBPC) trial of methylphenidate was performed as a clinical treatment programme as best clinical practice to determine the effects of methylphenidate and optimal dose compared with placebo<br>Conflicts of interest: no affiliations with pharmaceutical companies or similar stated |

*Forness 1992*

| Methods | Double-blind, placebo-controlled, cross-over trial with 2 interventions<br>1. Methylphenidate<br>2. Placebo<br>Phases: 4 |
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| Participants | Number of participants screened: 82<br>Number of participants included: 71 (all boys). Participants were randomly assigned to different possible drug condition orders of placebo and 3 doses of methylphenidate<br>Number of participants followed up: Conners' Teacher (n = 47), Conners' Parent (n = 69)<br>Number of withdrawals: Conners' Teacher 33.8%, Conners' Parent 12.6%<br>Diagnosis of ADHD: DSM-III-R (hyperactive-impulsive (100%))<br>Age: mean 9.3 years (range 7 to 11)<br>IQ: mean 106.2 (range 67 to 137)<br>Methylphenidate naive: 100%<br>Ethnicity: ethnic minority (11.3%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: conduct disorder (30/71)<br>Comedication: no; had no psychotropics for a month before<br>Sociodemographics: Alll participants were middle to upper class<br>**Inclusion criteria**<br>1. Boys<br>2. 7 to 11 years of age<br>3. Recruited from referrals to 2 clinics: University of California, Irvine Child Development Center for Children with ADD, and University of California, Los Angeles Child Psychiatry Outpatient Department for children with psychiatric disorders<br>4. Meet cutoff for inattention/overactivity<br>**Exclusion criterion**<br>1. IQ below 85 |
| Interventions | Participants were randomly assigned to different possible drug condition orders of 0.3, 0.6 and 1.0 mg/kg MPH (unless dosages would exceed 20 mg, so the low dose would be 0.15 mg/kg) 3 times a day and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: 3 times a day – 7:30 AM, 11:30 AM, 3:30 PM<br>Duration of each medication condition: 7 days<br>Washout before study initiation: not stated<br>Titration period: nil<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. Conners' Rating Scale: teachers and parents |
| Notes | Sample calculation: not stated<br>Ethics approval: not stated<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Key conclusion of study authors**<br>1. At the very least , teachers may be cautious about optimistic claims of positive response to methylphenidate<br>Email correspondence with study authors. Emailed study authors to ask for additional information but have not received a reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not stated |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Unclear risk | Reported as double-blind but not described |
| Blinding of outcome assessment (detection bias) | Unclear risk | Reported as double-blind but not described |
| Incomplete outcome data (attrition bias) | Unclear risk | Not stated<br>Selection bias (e.g. titration after randomisation → exclusion): no, but high loss to follow-up for teachers' scores on Conners' Teacher Rating Scale<br>Washout period between medication conditions: unclear |
| Selective reporting (reporting bias) | Unclear risk | Not clear |
| Vested interest bias | Low risk | Study supported by National Institute of Mental Health (NIMH) grant MH38686<br>Conflicts of interest: no affiliations described |

*Froehlich 2011*

| Methods | Randomised, double-blind, placebo-controlled, cross-over trial of multiple methylphenidate doses in stimulant-naive school-aged children<br>Phases: 3 active dosage weeks and 1 week of placebo |
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| Participants | Number of participants screened: 162<br>Number of participants included: 105. Participants were randomly assigned to 1 of 6 possible drug condition orders<br>Number of participants followed up: 89 (65 boys, 24 girls)<br>Number of withdrawals: 16<br>Diagnosis of ADHD: DSM-IV (combined (48%), hyperactive-impulsive (0%), inattentive (52%))<br>Age: mean 8.13 years (range 7 to 11)<br>IQ: mean: 105.34 ± 12.65<br>Methylphenidate naive: 100%<br>Ethnicity: Caucasian (79%), African American (18%), Hispanic (2%), other (1%)<br>Country: USA.<br>Setting: out-patient clinic<br>Comorbidity: anxiety disorder (17%), mood disorder (2%), disruptive behaviour disorder (36%)<br>Comedication: not stated<br>**Inclusion criteria**<br>1. ADHD according to DSM-IV criteria for onset age, pervasiveness and impairment, inattentive or combined type<br>2. Stimulant-naive<br>3. 7 to 11 years of age<br>4. 6 non-overlapping symptoms in a symptom domain (as per Diagnostic Interview Schedule for Children, and Vanderbilt ADHD Teacher Rating Scale), and both parent and teacher reported ≥ 4 symptoms in that domain<br>**Exclusion criteria**<br>1. Hyperactive-impulsive-type participants<br>2. IQ ≦ 80<br>3. Mania/hypomania<br>4. Comorbid oppositional defiant disorder, conduct disorder, depression and anxiety, if they were determined to be the primary cause of ADHD symptoms, or required different treatment<br>5. Medical history suggesting significant brain injury |
| Interventions | Participants were randomly assigned to 1 of 6 possible drug condition orders of OROS methylphenidate (18 mg, 27 mg, 36 mg for children ≤ 25 kg; 18 mg, 36 mg or 54 mg for children > 25 kg; sample mean maximum dose 1.57 mg/kg/d) and placebo<br>Administration schedule: once daily<br>Duration of each medication condition: 1 week<br>Washout before study initiation: drug naive<br>Medication-free period between interventions: not stated<br>Titration period: none initiated before/after randomisation<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. Parents and teachers: Vanderbilt ADHD Rating Scales: completed at baseline and each week of the trial |

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| Notes | Sample calculation: yes<br>Ethics approval: yes; Cincinnati Children's Hospital Institutional Review Board<br>**Comments from study authors**<br>1. Additional limitations include restricted duration of follow-up and heterogeneity of our sample due to recruitment from a variety of sources. Further, our sample had more inattentive (52%) than combined subtype (48%) participants<br>2. Although consistent with subtype distribution in many epidemiological samples, this differs from clinic settings, where combined type is most common<br>**Key conclusions of study authors**<br>1. Results of this double-blind, placebo-controlled, ADHD pharmacogenetic trial of psychostimulant-naive school-aged children suggest that dopamine active transporter (DAT) and dopamine receptor (DR) D4 variations may be associated with unique methylphenidate dose-response curves<br>2. Children lacking the DAT 10-repeat allele and those with the DRD4 4-repeat allele had a more robust methylphenidate response compared with those of alternate genotypes, consistent with improved response for the ADHD susceptibility low-risk alleles<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: no<br>Email correspondence with study author: October/November 2013. Contacted study author to obtain mean and SD for ADHD symptoms. Never received additional data. Therefore no further email correspondence regarding allocation concealment, randomisation, etc. |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomly assigned to different drug orders. No description about how |
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Blinding of participants and personnel (performance bias) | Unclear risk | Study medication consisted of identical capsules filled with an inert white powder (placebo) or prescribed dose of Concerta overencapsulated to preserve double-blind<br>Double-blind, but not specified who was blinded |
| Blinding of outcome assessment (detection bias) | Unclear risk | Study medication consisted of identical capsules filled with an inert white powder (placebo) or prescribed dose of Concerta overencapsulated to preserve double-blind<br>Double-blind, but not specified who was blinded |
| Incomplete outcome data (attrition bias) | Low risk | Data provided on 89 participants who completed the study |
| Selective reporting (reporting bias) | Unclear risk | Not able to find protocol or trial identifier |
| Vested interest bias | Low risk | National Institute of Mental Health (NIMH) and Cincinnati Children's Hospital Center for Education and Research Therapeutics Award<br>Conflicts of interest: Dr. Epstein receives funding from Eli Lilly and Co. Dr. Stein has received research support from Eli Lilly and Co., McNeil Pharmaceuticals, Novartis and Shire. He has served on a Speakers' Bureau for Novartis and has served as consultant to Novartis, Shire and Shinogi Pharmaceuticals |

*Gadow 1990*

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| **Methods** | Six-week double-blind, cross-over trial in which participants received the following in random order<br>1. Low dose of methylphenidate<br>2. Moderate dose of methylphenidate<br>3. Placebo<br>Furthermore, a single case report from the study is described |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 11 (11 boys, 0 girls). Participants were randomly assigned to 1 of 6 possible drug condition orders<br>Number of participants followed up: between 9 and 10, depending on ratings<br>Number of withdrawals: 1 to 2<br>Diagnosis of ADHD: DSM-III (type not stated)<br>Age: mean not reported (range 5.9 to 11.9 years)<br>Case report: 10 years of age<br>IQ: > 75<br>Stimulant-naive: 6<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: disruptive behaviour disorder<br>Comedication: not reported<br>Sociodemographics: Children represented a full range of socioeconomic backgrounds<br>**Inclusion criteria**<br>1. Boys<br>2. 5 to 12 years of age<br>3. ADHD diagnosis according to DSM-III<br>4. Scored above research cutoff (> 7) on the Aggression scale of IOWA Conners' Teacher Rating Scale OR were considered aggressive by their classroom teacher and were above cutoff on ≥ 1 other conduct problem scale<br>5. Scored ≥ 15 on the Abbreviated Teacher Rating Scale<br>6. Above cutoff on the Oppositional DIsorder or Conduct Disorder Index of the Parent or Teacher Version of the Stony Brook Child Psychiatric Checklist, Version 3<br>**Exclusion criteria**<br>1. IQ < 70<br>2. Psychosis, pervasive developmental disorder, dangerous to self or others<br>3. Seizure disorder, major organic brain dysfunction, medical illness, contraindication to medication treatment |
| **Interventions** | Participants were randomly assigned to 1 of 6 possible drug condition orders of low-dose (0.3 mg/kg) and moderate-dose (0.6 mg/kg) (upper limit 25 mg) methylphenidate and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: b.i.d., morning, noon, 3.5 hours apart, 7 days a week<br>Duration of each medication condition: 2 weeks<br>Washout before study initiation: yes<br>Titration period: When moderate dose was not preceded by low-dose condition, the child was gradually built up to the moderate dose. Data from these titration days were excluded from the analyses<br>Treatment compliance: pill count, no further information |

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| Outcomes | **ADHD symptoms**<br>1. Conners' Abbreviated Teacher Rating Scale<br>2. Conners' Abbreviated Parent Rating Scale<br>**Non-serious adverse events**<br>1. Stimulant Side Effects Checklist: rated systematically |
| Notes | Sample calculation: no information<br>Ethics approval: no information<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Comment from study authors**<br>1. Sample size was small, which decreased the probability of detecting clinically significant group differences between treatment conditions<br>**Key conclusion of study authors**<br>1. Results of this study indicate that methylphenidate-induced improvements in the classroom behaviour of aggressive hyperactive boys are associated with concomitant changes in the demeanor of classmates sitting in close proximity to the drug-treated child<br>Email correspondence with study authors: July 2013. Emailed first study author twice to get additional information (funding, ethics approval, etc.) and data from the study. Study authors not able to provide us with additional data |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Dose schedules were assigned on a random basis |
| Allocation concealment (selection bias) | Low risk | Medication and placebo pills were identical and were dispensed to parents and school nurses in dated, sealed envelopes |
| Blinding of participants and personnel (performance bias) | Low risk | Parents, teachers, observers, treating physicians and children were blinded to dose and order |
| Blinding of outcome assessment (detection bias) | Low risk | Parents, teachers, observers, treating physicians and children were blinded to dose and order |
| Incomplete outcome data (attrition bias) | Low risk | For classroom analyses, data on 10 boys were analysed, and for lunch room analyses, data on 9 boys were analysed<br>Selection bias (e.g. titration before randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | Email sent to first study author. No answer; therefore not able to get information |
| Vested interest bias | Unclear risk | Email sent to first study author in July 2013. No answer<br>Ciba Pharmaceutical Company supplied methylphenidate placebo<br>Conflicts of interest: not stated |

*Gadow 1995*

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| **Methods** | Randomised, placebo-controlled, double-blind, cross-over trial with 2 interventions<br>1. Methylphenidate in 2 or 3 dosages<br>2. Placebo<br>**Phases**<br>1. Washout if medications before trial<br>2. Eight-week randomised, controlled trial (RCT) with 2 weeks on each arm<br>3. Open-label follow-up at 24 months |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 34 (31 boys, 3 girls). Participants were randomly assigned to different orders of the 3 dosages<br>Number of participants followed up: RCT 34, MED (minimal effective dose, after RCT) 27; 12-month follow-up 30; 18-month follow up 26; 24-month follow-up 26<br>Number of withdrawals: RCT: 0<br>Diagnosis of ADHD: DSM-III-R (subtypes not stated)<br>Age: mean 8 years and 10 months (range 6.1 years to 11.9 years)<br>IQ: mean 105.9 (SD 13.7, range no information)<br>Methylphenidate naive: 24 (71%)<br>Ethnicity: Caucasian (85%), African American (3%), Asian (3%), Hispanic (9%), other (0%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: Data from only 21 children from Gadow et al. (1995): tics (100%); anxiety or depressive disorder, or both (8/21; 38%); obsessive-compulsive disorder (3/2; 14%); most of the children also had oppositional defiant disorder or conduct disorder and academic problems<br>Comedication: not during RCT. Four children were treated with an anti-tic medication in combination with methylphenidate at some time during the course of follow-up (neuroleptic 3, clonidine 1)<br>Sociodemographics: no information<br>**Inclusion criteria**<br>1. Meet DSM III-R diagnostic criteria for ADHD and chronic motor tic disorder or Tourette's disorder<br>2. ADHD had to be a primary reason for seeking clinical services<br>3. In general, had to be above the cutoff on 2 or 3 parent- and teacher-rated hyperactivity and/or ADHD behaviour rating scales<br>4. Written signed statement from parents consenting to their child’s participation<br>**Exclusion criteria**<br>1. Dangerous to self or others<br>2. Tics: the major clinical management concern<br>3. Psychosis<br>4. IQ < 70<br>5. Seizure disorder<br>6. Major organic brain dysfunction<br>7. Major medical illness<br>8. Contraindications to medication (other than tics)<br>9. Pervasive developmental disorder |

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| Interventions | Participants were randomly assigned to 1 of 4 possible drug condition orders of doses: 0.1 mg/kg (mean 4.4 mg), 0.3 mg/kg (mean 9.0 mg) and 0.5 mg/kg (mean 14.0 mg) of methylphenidate and placebo<br><br>Upper dosage limit was 20 mg. When the 0.5-mg/kg dose was not preceded by a low-dose condition, the child was gradually built up to the moderate dose. Build-up days occasionally fell on scheduled school observation days. Observers were unaware of these days and observations were conducted as usual, but these data were excluded from the analyses<br><br>Administration schedule: b.i.d. (or t.i.d.) at morning and noon, approximately 3.5 hours apart, 7 days a week<br><br>Duration of each medication condition: 2 weeks<br><br>Washout before study initiation: methylphenidate 1 week, antipsychotic 3 weeks, clonidine 2 weeks<br><br>Medication-free period between interventions: none<br><br>Titration period: none<br><br>Treatment compliance: Parents and nurses were asked to return unused medication envelopes, which allowed researchers to assess compliance. No further information was provided in the paper<br><br>Regarding 24-month follow-up: Total daily dose of methylphenidate, MED (minimal effective dose - after RCT) mean 16.5 mg (range 5 mg to 40 mg); second visit mean 28.5 mg (range 15 mg to 60 mg); third visit mean 29.2 mg (range 10 mg to 90 mg); and fourth visit mean 34.5 mg (range 15 mg to 92 mg) |

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| Outcomes | During 8-week RCT<br>**ADHD symptoms**<br>1. Parents<br>a. Conners' Abbreviated Parent Rating Scale: rated Saturday and Sunday each week<br>b. Mothers' Objective Method for Subgrouping: rated by parents Saturday and Sunday each week<br>2. Teachers<br>a. Conners' Abbreviated Teacher Rating Scale, 10-item: rated 2 days per week for each intervention period<br>b. Iowa Conners' Teacher Rating Scale: rated 2 days per week for each intervention period<br>**General behaviour**<br>1. Peer Conflict Scale: parent- and teacher-rated, 2 times a week<br>2. Classroom Observation Code: observer-rated, 4 days for each treatment condition<br>3. ADHD School Observation Code: observer, 3 to 4 days for each treatment condition<br>4. Code for Observing Social Activity: observer, lunch and playground, 20 to 30 minutes, 4 days for each treatment condition<br>**Non-serious adverse events**<br>1. Side Effects Checklist: 13 items, rated by parents on Saturday and Sunday and rated by teacher twice a week<br>2. Global Tic Rating Scale: rated by parents on Saturday and Sunday and rated by teacher twice a week<br>3. Motor and vocal tic category: Observers coded presence or absence of tics in the classroom, lunchroom or playground, 4 times for each medication condition<br>**Physician evaluations**<br>1. Yale Global Tic Severity Scale: rated every second week<br>2. Tourette Syndrome Unidentified Rating Scale: rated every second week<br>3. Global Tic Rating Scale (assessed in only 22 participants): rated every second week<br>4. Shapiro Tourette Syndrome Severity Scale (assessed in only 22 participants): rated every second week<br>5. Motor tic frequency tics: rated in 180 five-second intervals in a simulated classroom; tics were coded as present or not present in each interval, rated every second week<br>6. Weight: assessed every second week<br>7. Heart rate: assessed every second week<br>8. Blood pressure: assessed every second week<br>During 24-month follow-up<br>**Physician evaluations**<br>1. All rated at minimally effective dose (right after RCT) 6 months, 12 months, 18 months and 24 months<br>2. Yale Global Tic Severity Scale<br>3. Shapiro Tourette Syndrome Severity Scale<br>4. Three subscales from Tourette Syndrome Unified Rating Scale<br>5. Total number of tics<br>6. Number of tics observed in 2 minutes of quiet conversation with physician<br>7. LeWitt Disability Scale, which assesses tics and symptoms of comorbidity<br>8. Global Tic Rating Scale<br>9. Blood pressure<br>10. Heart rate<br>11. Pulse<br>12. Weight<br>**Parent ratings**<br>1. Based on last 2 weeks and rated at MED (right after RCT) 6 months, 12 months, 18 months and 24 months<br>2. Stimulant Side Effects Checklist<br>3. Global Tic Rating Scale |

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| Notes | Sample calculation: yes<br><br>Ethics approval: no information<br><br>**Comments from study authors**<br><br>1. Magnitude of clinical improvement associated with 0.3 mg/kg dosage vs 0.5 mg/kg dosage was generally trivial for many children<br>2. 0.5 mg/kg dosage was associated with more side effects, but fortunately they were generally of limited clinical significance<br>3. Generalisability of findings from this study is subject to several qualifications. First, our data pertain to observed treatment effects over an 8-week period and therefore cannot address the issue of tic exacerbation as a function of long-term drug exposure. Furthermore, the findings pertain only to children with ADHD with tics of mild to moderate severity that occur frequently enough to be observed during 15-minute intervals<br><br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no; children were not excluded from participation in the study if they had prior experience with stimulant drug therapy, or if such therapy purportedly had exacerbated their tics<br><br>Any withdrawals due to adverse events: no<br><br>**Key conclusions of study authors**<br><br>1. During the course of this short-term drug evaluation, physician, teacher and parent ratings were in agreement that methylphenidate did not lead to worsening of the severity of children's tic disorders<br>2. Methylphenidate is an effective drug for the treatment of ADHD and oppositional and aggressive behaviour<br>3. Follow-up study showed that long-term treatment with methylphenidate seems to be safe and effective for the management of ADHD behaviours in many (but not necessarily all) children with mild to moderate tic disorders. Nevertheless, careful clinical monitoring is mandatory, to rule out the possibility of drug-induced tic exacerbation in individual patients<br><br>**Comments from study authors (limitations)**<br><br>1. Two-year follow-up component was not blinded. Although obstacles to creating and maintaining a long-term double-blind study with a placebo group are daunting, failure to do so does introduce the possibility of bias<br>2. Absence of a no-treatment group does not allow inferences about natural changes in tic status over time<br><br>**Comments from review authors**<br><br>1. Well-designed study<br>2. No exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate. Twenty-six children received stimulant medication throughout the follow-up interval; of these children, 1 was switched to dextroamphetamine. However, we have chosen to use in our analyses results for all 26<br>3. In the article, "Gadow 2001, Anxiety and Depression…", n = 38. We have included it because it is part of the study, but we have not used data from this article<br>4. Sverd 1992 and Gadow 1992; preliminary results from Gadow 1996 are described<br>5. All included articles include a mix of different protocols, so total numbers of included participants differ from article to article<br><br>Email correspondence with study authors: April 2013. We emailed study authors for supplemental information regarding cross-over data. Data were not available. Also no further data for the interventions were available |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Dose schedules were counterbalanced and assigned on a random basis |
| Allocation concealment (selection bias) | Low risk | Medication and identically matching placebos were dispensed to parents and school nurses in dated, sealed envelopes at 2-week intervals |
| Blinding of participants and personnel (performance bias) | Low risk | Parents, teachers, participants, observers and physicians were blinded to the identity of those conditions |
| Blinding of outcome assessment (detection bias) | Low risk | Medication was administered under double-blind conditions (i.e. no one involved in clinical management of the participant, data collection or interaction with the school knew the identity of treatment conditions) |
| Incomplete outcome data (attrition bias) | Low risk | Study describes how many people were included in the different analyses<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Unclear risk | No protocol identified or received |
| Vested interest bias | Low risk | Research grants from the Tourette Syndrome Association and the National Institute of Mental Health (NIMH)<br>Conflicts of interest: not stated |

### *Gadow 2007*

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| Methods | Double-blind, randomised, cross-over trial with interventions<br>1. Methylphenidate<br>2. Placebo<br>**Phases**<br>1. Washout if previously medicated<br>2. Eight-week trial, 2 weeks on each arm. Performed in 2 cohorts (several years apart, same personnel) |

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| Participants | Number of participants screened: not stated<br>Number of participants included: 71 (39 + 32, cohorts 1 and 2, respectively). Participants were randomly assigned to 1 of 4 possible drug condition orders<br>Number of participants followed up: 71 (57 boys, 14 girls)<br>Number of withdrawals: not stated<br>Diagnosis of ADHD: DSM-III-R or DSM-IV (subtype not stated)<br>Age: mean: 8.9 ± 1.9 years (range 6 to 12)<br>IQ: mean 103.8<br>Methylphenidate naive: not stated<br>Ethnicity: Caucasian (87%), African American (6%), Asian (1%), Hispanic (6%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: Tourette's syndrome (96%), chronic motor tic disorder (4%), oppositional defiant disorder (56%), conduct disorder (7%), overanxious or generalized anxiety (30%), simple phobia (7%), obsessive-compulsive disorder (11%)<br>Comedication: yes<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. DSM-III-R or DSM-IV diagnosis of ADHD<br>2. Chronic motor tic disorder or Tourette's syndrome<br>3. ADHD clinical criteria at both school and home<br>**Exclusion criteria**<br>1. Too severely ill (dangerous to self or others)<br>2. Psychotic<br>3. IQ < 70<br>4. Seizure disorder<br>5. Major organic brain dysfunction<br>6. Major medical illness<br>7. Medical or other contraindication to medication (other than tics)<br>8. Pervasive developmental disorder<br>9. Tics so severe at intake that the parent or the child requested immediate intervention<br>10. Extremely mild tics at intake |
| Interventions | Participants were randomly assigned to placebo or to 1 of 3 possible drug condition orders of immediate-release methylphenidate (0.1 mg/kg (mean 4.5 mg; SD 1.6), 0.3 mg/kg (mean 9.3 mg; SD 3.0) and 0.5 mg/kg (mean 14.3 mg; SD 3.3)), twice a day for 2 weeks, each under double-blind conditions. Upper limit was 20 mg/d<br>Administration schedule: twice daily, 3.5 hours apart. Most days, a morning dose and a noon dose, 7 days a week<br>Duration of each medication condition: 2 weeks<br>Washout before study initiation: Minimum washout periods for children receiving medication at referral were as follows: 1 week for stimulants (n = 10), 3 weeks for neuroleptic or selective serotonin reuptake inhibitor (n = 2) and 2 weeks for clonidine (n = 1)<br>Medication-free period between interventions: none<br>Titration period: not stated initiated before/after randomisation<br>Treatment compliance: not stated |

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| Outcomes | **ADHD symptoms**<br>1. Teachers<br>a. Abbreviated Teacher Rating Scale (total score (Hyperkinesis Index) and ADHD (factor 1) and Emotional lability (factor 2) subscales)<br>b. IOWA Conners' Teacher Rating Scale (Inattention-Impulsivity-Overactivity and Oppositional Defiant subscales): twice a week, weekdays<br>2. Parents<br>a. Abbreviated Parent Rating Scale (Total score (Hyperkinesis Index) and ADHD (factor 1) and Emotional lability (factor 2) subscales): Saturdays and Sundays, every week<br>**General behaviour**<br>1. IOWA Conners' Teacher Rating Scale (Oppositional Defiant subscale)<br>**Non-serious adverse events**<br>1. Physician<br>a. Assessment of clinical status and heart rate, blood pressure and weight: biweekly (n = 57)<br>b. Tics: Yale Global Tic Severity Scale (includes 4 behaviourally anchored subscales: Total Motor Tic score, Total Phonic Tic score, Overall Impairment Rating and Global Severity score), completed for all but the first 12 participants. Additional measures: Shapiro Tourette Syndrome Severity Scale (tic frequency, severity and impairment), Global Tic Rating Scale and Two-Minute Tic and Habit Count, completed for first 12 participants only. Both rated at 2-week intervals<br>2. Parents and teachers<br>a. Global Tic Rating Scale: twice a week for each week of the study<br>b. Stimulant Side Effects Checklist: rated twice a week |
| Notes | Sample calculation: no<br>Ethics approval: yes<br>**Comment from study authors**<br>1. Children were not excluded if previous treatment with stimulants had purportedly induced or exacerbated their tics<br>**Key conclusion of study authors**<br>1. In this study, immediate-release methylphenidate was found to be a safe and effective short-term treatment for ADHD in children with chronic tic disorder (CTD), but complete normalisation of all problem behaviours often is not achieved at acceptable doses<br>**Comments from review authors**<br>1. Given our concern about the possibility of a type II error (i.e. erroneously concluding that methylphenidate did not have an adverse effect on tics), follow-up repeat-measure ANOVAs were performed on each respondent category, even when the main effect of dose was not significant<br>2. Use of a cross-over design may result in carry-over effects. However, differences in change scores for tic frequency (simulated classroom) and severity (Yale Global Tic Severity Scale - Global Severity score), respectively, between baseline and placebo in children who received placebo first and last were non-significant and minuscule (i.e. effect size = 0.08 and 0.19, respectively)<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: April 2014. We obtained supplemental information from study authors |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Dose schedules were counterbalanced and assigned on a random basis |
| Allocation concealment (selection bias) | Low risk | Medication was administered twice daily, approximately 3.5 hours apart, 7 days per week, and was dispensed in dated, sealed envelopes at 2-week intervals |
| Blinding of participants and personnel (performance bias) | Low risk | Double-blind conditions |
| Blinding of outcome assessment (detection bias) | Unclear risk | No information |
| Incomplete outcome data (attrition bias) | Low risk | None required withdrawal of medication |
| Selective reporting (reporting bias) | Unclear risk | No information to assess this |
| Vested interest bias | Low risk | This study was supported in part by a research grant from the Tourette Syndrome Association Incorporated, and by Public Health Service (PHS) grant number MH45358 from the National Institute of Mental Health (NIMH)<br>Conflicts of interest: Study authors have no financial relationships to disclose |

*Gadow 2011*

| Methods | Eight-week, placebo-controlled, cross-over trial with 2 interventions<br>1. Methylphenidate<br>2. Placebo |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 54 (42 boys, 12 girls). Participants were randomly assigned to the different possible drug condition orders: ADHD without anxiety 37, ADHD with anxiety 17<br>Number of participants followed up: not stated<br>Number of withdrawals: not stated<br>Diagnosis of ADHD: DSM-III or DSM-IV (subtype not stated)<br>Age: ADHD without anxiety 8.9 years, ADHD with anxiety 9.1 years (range 7 to 12)<br>IQ: ADHD without anxiety mean 103.5, ADHD with anxiety mean 103.1<br>Methylphenidate naive: 48 (89%)<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: Tourette's (n = 52), chronic multiple tic disorder (n = 2), anxiety (n = 17), major depressive episode or dysthymia (n = 11), overanxious disorder or generalised anxiety disorder (n = 12), separation disorder (n = 6), social phobia (n = 1), oppositional defiant disorder (n = 36), conduct disorder (n = 4)<br>Comedication: not stated<br>Sociodemographics: ADHD without anxiety 37.1, ADHD with anxiety 35.4 (according to Hollingshead)<br>**Inclusion criteria**<br>1. DSM-III-R or DSM-IV diagnostic criteria for ADHD<br>2. Chronic multiple tic disorder or Tourette's disorder according to research diagnostic criteria<br>3. Each child met ADHD clinical criteria at both school and home (the "and rule")<br>**Exclusion criteria**<br>1. Tics were the major clinical management concern<br>2. Too severely ill (dangerous to self or others)<br>3. Psychotic<br>4. Mentally retarded (IQ < 70)<br>5. Seizure disorder<br>6. Major organic brain dysfunction<br>7. Major medical illness<br>8. Medical or other contraindication to medication (other than tics)<br>9. Pervasive developmental disorder |
| Interventions | Participants were randomly assigned to different possible drug condition orders of 0.1 mg/kg, 0.3 mg/kg and 0.5 mg/kg methylphenidate and placebo<br>Mean methylphenidate dosage: 4.7 mg, 9.5 mg, 14.5 mg<br>Administration schedule: "administered twice daily, approximately 3.5 hours apart, 7 days a week"<br>Duration of each medication condition: 2 weeks<br>Washout before study initiation: not stated<br>Medication-free period between interventions: none<br>Titration period: none<br>Treatment compliance: not stated |

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| Outcomes | **ADHD symptoms**<br>1. Abbreviated Teacher/Parent Rating Scale<br>2. IOWA Conners' Teacher Rating Scale<br>3. Conners' (48-item) Parent Rating Scale<br>4. Mothers' Objective Method for Subgrouping<br>5. Parent and Teacher Versions of the Child Symptom Inventory<br>**General behaviour**<br>1. IOWA Conners' Teacher Rating Scale (Oppositional Defiant subscale)<br>**Non-serious adverse events**<br>1. Stimulant Side Effects Checklist<br>2. Yale Global Tic Severity Scale, which includes 4 behaviourally anchored subscales: Total Motor Tic score, Total Phonic Tic score, Overall Impairment Rating and Global Severity score |
| Notes | Sample calculation: not stated<br>Ethics approval: yes; approved by a university Institutional Review Board (IRB)<br>**Comments from study authors**<br>1. No evidence suggested that immediate-release methylphenidate exacerbated tics in children with anxiety<br>2. Teacher ratings actually indicated improvement in motor and vocal tic frequency with medication (placebo > 0.5 mg/kg)<br>**Key conclusions of study authors**<br>1. Findings suggest that the co-occurrence of diagnosed chronic multiple tic disorders and ADHD with anxiety represents a particularly troublesome clinical phenotype, at least in the home setting<br>2. Comorbid anxiety disorder was not associated with a less favourable response to immediate-release methylphenidate in children with ADHD and chronic multiple tic disorder, but replication with larger samples is warranted before firm conclusions can be drawn about potential group differences<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: May 2015. Emailed study authors requesting additional information but have not received a reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Dose schedules were counterbalanced and were assigned on a random basis |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | "...dispensed in dated, sealed envelopes at two-week intervals" |
| Blinding of outcome assessment (detection bias) | Unclear risk | No information |
| Incomplete outcome data (attrition bias) | Unclear risk | No information |
| Selective reporting (reporting bias) | Unclear risk | "In order to increase sample homogeneity, an additional three children with diagnosed specific phobia (n = 2) or major depressive episode without comorbid anxiety disorder (n = 1) were excluded from data analyses" |
| Vested interest bias | Low risk | Study was funded by the National Institute of Mental Health (NIMH) and the Tourette Syndrome Association Incorporated. CIBA Pharmaceutical Company supplied methylphenidate placebos. Novartis supplied immediate-release methylphenidate<br>Conflicts of interest: "Kenneth D. Gadow is a shareholder in Checkmate Plus, publisher of the Child Symptom Inventory-4" |

*Garfinkel 1983*

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| Methods | Double-blind, randomised, placebo-controlled, cross-over experiment with 4 arms<br>1. Methylphenidate<br>2. Clomipramine<br>3. Desipramine<br>4. Placebo<br>Study lasted 20 weeks; first and last 2 weeks were baseline periods during which no medication was given. Different interventions lasted 3 weeks each (Monday to Friday) with a 7-day washout between changes in drugs |

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| Participants | Number of participants screened: not stated<br>Number of participants included: 12 (all boys). Participants were randomly assigned to the different possible drug condition orders<br>Number of participants followed up: 12<br>Number of withdrawals: 0<br>Diagnosis: DSM-III of ADD. Eight participants were day hospital patients and 4 were in-patients<br>Age: mean 7.3 years (range 5.9 to 11.6)<br>IQ: > 70<br>Methylphenidate naive: 50%<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic and patient ward<br>Comorbidity: no<br>Comedication: no comedication during study period<br>Sociodemographics: not stated. Children presented with remarkably similar clinical, family and educational histories. None of the children had localising neurological signs or met criteria for other psychiatric diagnoses<br>**Inclusion criterion**<br>1. ADD according to DSM-III<br>**Exclusion criteria**<br>1. None mentioned directly |
| Interventions | Participants were randomly assigned to the different possible drug condition orders of methylphenidate, clomipramine, desipramine and placebo<br>Mean methylphenidate dosage: 18 mg/d<br>Administration schedule: b.i.d., morning and lunch<br>Duration of each medication condition: 3 weeks<br>Washout before study initiation: 2 weeks before study entry and 7 days between drug conditions<br>Titration period: first week of the drug condition after randomisation<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. Conners' Teacher Rating Scale: rated daily by care workers (in settings away from the classroom) and teachers (in classroom)<br>**General behaviour**<br>1. Werry-Weiss-Peters Activity Rating Scale: rated daily by parents for day patients and by evening child care staff for fully hospitalised children<br>**Non-serious adverse events**<br>1. Diastolic and systolic blood pressure, measured by the nurse while participants were sitting and standing at 09.00 AM and 12.00 PM<br>2. Apical pulse, morning and afternoon |

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| **Notes** | Sample calculation: no information<br>Ethics approval: no information<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Key conclusions of study authors**<br>1. Methylphenidate was significantly better for improving classroom and behavioural manifestations of ADD as compared with placebo, desipramine and clomipramine<br>2. Tricyclic antidepressants may have a significant therapeutic effect as indicated by mood elevation and amelioration of non-classroom behaviour in the evenings<br>3. Results encourage further clinical and pharmacological investigation of ADD using various alternative treatments<br>**Comment from review authors**<br>1. Only information and data extracted from the methylphenidate group and the placebo group<br>Email correspondence with study authors. October 2013. We obtained supplemental information regarding number of drop-outs and SD for Conners' Rating Scale. We also wanted other data but were not able to obtain these, as the study took place several years ago and the data are no longer available |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Children were randomly given methylphenidate, desipramine, clomipramine, placebo<br>A Latin square was followed to control for the order of presentation of drugs |
| Allocation concealment (selection bias) | Low risk | Children were randomly given MPH, DMI, CMI, placebo. A Latin square was followed to control for the order of presentation of drugs |
| Blinding of participants and personnel (performance bias) | Low risk | Participants, parents, attending physicians, teachers, nursing staff and child care workers did not know which medication the child received, ensuring the double-blind procedure. Medication was added to lactose powder and was placed in identical appearing gelatin capsules |
| Blinding of outcome assessment (detection bias) | Low risk | Participants, parents, attending physicians, teachers, nursing staff and child care workers did not know which medication the child received, ensuring the double-blind procedure. Medication was added to lactose powder and was placed in identical appearing gelatin capsules |
| Incomplete outcome data (attrition bias) | Unclear risk | No information |
| Selective reporting (reporting bias) | Low risk | No reporting bias |
| Vested interest bias | Low risk | Study was funded by Ontario Mental Health Foundation<br>Conflicts of interest: none |

*Gonzalez-Heydrich 2010*

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| **Methods** | Cross-over trial with 2 interventions<br>1. OROS methylphenidate<br>2. Placebo<br>Phases: Number of phases varied by dose group. For all dose groups, after completing first phase, participants were on a 1-week washout period before cross-over. Participants assigned to 1 of 3 maximum OROS methylphenidate dose groups in randomly assigned order<br>1. Group 1: 1 week low dose, 1 week placebo<br>2. Group 2: 1 week low dose, 1 week medium dose, 1 week placebo<br>3. Group 3: 1 week low dose, 1 week medium dose, 1 week high dose, placebo<br>Participants assigned to next group after 3 participants have successfully completed preceding group with no side effects |
| **Participants** | Number of participants screened: 40<br>Number of participants included: 33 (19 boys, 14 girls). Participants were randomly assigned to different possible drug condition orders<br>Number of participants followed up: 33<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-IV-R (combined (51.1%), inattentive (48.5%))<br>Age: mean 10.5 years (SD 3.0, range 6.4 to 17.5)<br>IQ: mean 89.7 (SD 16.9, range 59 to 123)<br>Methylphenidate naive: not stated<br>Ethnicity: not stated<br>Country: USA<br>Setting: hospital ward<br>Comorbidity: epilepsy (100%), others (not stated)<br>Comedication: yes<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Speaks English<br>2. IQ > 35 and score > 35 on Scales of Independent Behavior Revised (SIB-R) Broad Independence Scale (both IQ and adaptive functioning at the moderate mental retardation level or higher)<br>3. Diagnosis of epilepsy by International League Against Epilepsy (ILEA) criteria 26 (repeated, afebrile, unprovoked seizures with a seizure within the past 5 years)<br>4. *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV-R diagnosis of ADHD<br>5. Score ≥ 4 on Conners' Global Index (CGI) severity scale for ADHD<br>6. Score > 90% on ADHD Rating Scale, Parent Version; investigator scored for age and sex on inattentive, hyperactive-impulsive or total score at first visit<br>7. Has not taken stimulants or alpha-adrenergic medications for longer than 2 weeks before study entry<br>8. If taking antidepressants, neuroleptics or lithium, doses have been stable for longer than 4 weeks<br>9. Currently on an antiepileptic drug regimen with stable doses for longer than 4 weeks before study entry<br>10. Seizure-free for longer than 1 month before study entry<br>11. Prescribing clinician for epilepsy anticipates the need for a stable antiepileptic drug regimen for the duration of the study<br>12. Guardian gives permission for study personnel to communicate with prescribing epilepsy clinician<br>13. Teacher agrees to fill out ADHD Rating Scale at baseline and at the end of each arm of the study<br>**Exclusion criteria**<br>1. Has had a seizure within the month preceding study entry<br>2. Change in antiepileptic drug regimen or dose within 4 weeks of study entry<br>3. History of moderate or severe adverse event related to methylphenidate |

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| | 4. History of any psychotic disorder<br>5. Current acute major depression or bipolar mania<br>6. Current psychiatric disorder requiring pharmacotherapy (other than ADHD)<br>7. Unstable significant medical condition other than epilepsy<br>8. Any known conditions that may make treatment with methylphenidate medically inadvisable<br>9. Not currently working with a physician for epilepsy treatment<br>10. Previously participated in a trial that provided adequate treatment with extended-release methylphenidate<br>11. Weighs < 9 kg<br>12. Pregnant<br>13. Unwilling to use an effective form of contraception<br>14. Child has taken a stimulant (methylphenidate, an amphetamine preparation or pemoline), an alpha-adrenergic (clonidine or guanfacine) or other ADHD medication within 2 weeks of the screening telephone interview (children will not be withdrawn from psychotropic medications to be enrolled in the study) |
| Interventions | Participants were randomly assigned to different possible drug condition orders of methylphenidate and placebo. Each patient was given 5 mg of immediate-release methylphenidate in the morning and at noon for 1 day. If this dose was tolerated, 18 mg of OROS methylphenidate was administered in the morning for the remaining 6 days of the first week. For group 1, maximum dose remained 18 mg, and methylphenidate and placebo arms lasted 1 week. For group 2, a further 1 week of OROS methylphenidate at a dose of 36 mg was given in the morning for 1 week; this group was also administered placebo for 2 weeks. For group 3, maximum dose was 54 mg in the morning, and each arm of the cross-over lasted 3 weeks<br>Mean methylphenidate dosage: 11 participants < 1 mg/kg/d, 13 participants 1 to 1.5 mg/kg/d, 9 participants 1.5 to 2 mg/kg/d<br>Administration schedule: 1 dose in the morning<br>Duration of each medication condition: 1 week<br>Washout before study initiation: not stated<br>Medication-free period between interventions: yes; 1 week<br>Titration period: no<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. ADHD Rating Scale, Fourth Edition, Observer, Parent, Teacher Version; Conners' Global Index (CGI)-ADHD-Severity: clinician-rated at baseline and at end of each cross-over week<br>**Serious adverse events**<br>1. Seizure Classification Interview: observer, baseline and during trial<br>**Non-serious adverse events**<br>1. Barkley Side Effects Checklist - Modified: observer, each study visit |

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| **Notes** | Sample calculation: no<br>Ethics approval: not stated<br>**Comment from study authors**<br>1. Considering exposure time, we observed increased daily risk of seizures with increasing dose of OROS methylphenidate, suggesting that potential safety concerns require further study<br>**Key conclusions of study authors**<br>1. No serious adverse events and no carry-over effects were noted in the cross-over trial<br>2. A larger study is needed to assess the effect of OROS methylphenidate on seizure risk<br>3. Cross-over design, including participants with frequent seizures, could maximise power and address high participant heterogeneity and recruitment difficulties<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes<br>Email correspondence with study authors: April 2014. We obtained supplemental efficacy data from study authors |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomisation lists for each maximum dose group were prepared by a statistician and maintained by the research pharmacist |
| Allocation concealment (selection bias) | Low risk | Randomisation lists for each maximum dose group were prepared by a statistician and maintained by the research pharmacist |
| Blinding of participants and personnel (performance bias) | Low risk | Participants were randomly assigned to take OROS methylphenidate or placebo. Principal investigator was blind to medication status. In cases of seizure worsening... Data and Safety Monitoring Board (DSMB) and Institutional Review Board (IRB) were informed of these seizures. Study personnel, the DSMB and the IRB were not unblinded through this process, as the participant would not be exposed again to the same condition |
| Blinding of outcome assessment (detection bias) | Low risk | Principal investigator was blinded to medication status |
| Incomplete outcome data (attrition bias) | Unclear risk | Five participants discontinued treatment while taking placebo and 14 while taking OROS methylphenidate; however, all were included in all analyses<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | High risk | All outcomes reported referred to parent- and teacher-rated versions of ADHD Rating Scale, Fourth Edition, and to clinician-rated ADHD Severity measured weeks 1 to 4 in the protocol. Barkley Total scores (although significantly different) were not reported, although individual effects were reported |
| Vested interest bias | Unclear risk | Supported by National Institute of Mental Health (NIMH) Grant, Number K23 MH066835<br>Conflicts of interest: Four study authors are involved in the pharmaceutical sector |

*Gorman 2006*

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| **Methods** | Participants with ADHD took part in a randomly ordered, double-blind, cross-over clinical drug trial comprising 21 consecutive days of<br>1. Methylphenidate<br>2. Placebo |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 43<br>Number of participants followed up: 41 (21 boys, 20 girls)<br>Number of withdrawals: 2<br>Diagnosis of ADHD: DSM-IV (combined (n = 22), hyperactive-impulsive (n = 0), inattentive (n = 19))<br>Age: mean 9.08 years (range 6.26 to 12.55)<br>IQ: mean 107.66<br>Methylphenidate naive: 37 (out of 41)<br>Ethnicity: Caucasian (92.67%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: > 2 anxiety disorders (12.16%), lifetime affective disorder (2.46%), oppositional defiant disorder or conduct disorder (49.28%)<br>Comedication: 0%<br>Sociodemographics: mean 50.43 (range 22 to 66) (Hollingsworth SES)<br>**Inclusion criteria**<br>1. 6 to 12 years of age<br>2. Diagnosis of ADHD according to DSM-IV, and based on a combination of the Parent Interview for Child Symptoms-4 and a semi structured interview<br>3. IQ > 80<br>4. Normal or corrected vision and hearing<br>5. No current use of medicine<br>**Exclusion criteria**<br>1. Physical disabilities; history of neurological disorder, chronic medical illness, bipolar disorder, schizophrenia or pervasive developmental disorder; and an episode of major depressive disorder within at least 6 months |
| **Interventions** | Participants were randomly assigned to 1 dose of methylphenidate and placebo<br>Mean methylphenidate dosage: final daily dose 33.12 mg ± 1.36 (SE), range 25 to 50 mg/d (0.94 ± 0.02 mg/kg)<br>Administration schedule: b.i.d.<br>Duration of each medication condition: 21 days<br>Washout before study initiation: not stated<br>Medication-free period between interventions: from lunch to the following morning<br>Titration period: 0.25 mg/kg b.i.d. (breakfast and lunch) on days 1 to 2; 0.25 mg/kg b.i.d. plus 0.125 mg/kg at 4:00 PM on days 3 to 7; 0.3 mg/kg b.i.d. and 0.15 mg/kg at 4:00 PM on days 8 to 14; and 0.4 mg/kg b.i.d. and 0.2 mg/kg at 4:00 PM on days 15 to 21. All dosages were administered to the nearest 2.5 mg<br>Titration: took place after randomisation<br>Treatment compliance: not stated. Four participants with ADHD had undergone previous trials of stimulant therapy ranging from 2 weeks to 7 months |

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| Outcomes | **ADHD symptoms**<br>1. IOWA Conners' Scale, teacher- and parent-rated: at the end of each treatment period (around day 21)<br>**Serious adverse events**<br>1. Five participants with 'serious side effects' were referred to, but no further information was given<br>**Non-serious adverse events**<br>1. Barkley and Murphy Side Effects Rating Scale, rated by an investigator, at the end of each treatment<br>2. Weight, in street clothes and without shoes on a professional scale, at the end of each treatment period |
| Notes | Sample calculation: not described.<br>Ethics approval: yes<br>**Comment from study authors**<br>1. "The unusually high proportion of girls reflects increasing sensitivity by clinicians to the identification of girls with ADHD as well as the awareness of our referring sources that we were studying sex differences in ADHD"<br>**Key conclusions of study authors**<br>1. ADHD subtypes benefited comparably from methylphenidate treatment with respect to inattention<br>2. Children with ADHD-combined subtype underwent greater reductions in hyperactivity/impulsivity, but children with ADHD-inattentive subtype also benefited in this respect<br>3. Only children with ADHD/C displayed a reduction in externalising problems under methylphenidate. ADHD subtypes reacted comparably with stimulant treatment with respect to arithmetic performance, valence of teacher and parent comments and task-incompatible behaviours - all measures that do not distinguish between inattention, hyperactivity/impulsivity or oppositionality<br>4. Somatic effects of treatment were comparable for subtypes<br>**Comment from review authors**<br>1. Chang et al. 2001 (in Gorman 2006) is a PhD thesis; the other 2 articles are based on data from this. We have not had access to the full thesis<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: January 2014. We obtained supplemental information from study authors. Study authors do not have the files anymore; therefore we are not able to obtain all of the data requested |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Answer from study author: "Table of random numbers were used to make the allocation process, such that numbers ending in an even digit corresponded to one order and those ending in an odd digit to another" ( Krogh 2014c [pers comm] |
| Allocation concealment (selection bias) | Low risk | Answer from study author: "Table of random numbers were used to make the allocation process, such that numbers ending in an even digit corresponded to one order and those ending in an odd digit to another" ( Krogh 2014c [pers comm] |
| Blinding of participants and personnel (performance bias) | Low risk | Placebo capsules, identical in appearance and taste to those containing methylphenidate, and administered on the same schedule |
| Blinding of outcome assessment (detection bias) | Low risk | Second author blinded. Placebo capsules, identical in appearance and taste to those containing methylphenidate, and administered on the same schedule |
| Incomplete outcome data (attrition bias) | Low risk | When parents reported serious side effects (n = 5), their children's dosages were reduced, or planned increments were omitted. However, study authors noted "eliminating participants who could not tolerate their assigned dosage might potentially skew the sample"<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Low risk | No<br>Answer from study author: "Event related potentials and performance measures on a cognitive task were not reported (I didn't attempt to publish the ERP data because the analyses I conducted did not yield significant results) - And since we do not look at this outcome, we see it as low" ( Krogh 2014c [pers comm]) |
| Vested interest bias | Low risk | National Institute of Mental Health (NIMH)<br>Conflicts of interest: Study authors have no financial relationships to declare |

### *Green 2011*

| Methods | One-day, randomised, parallel trial with 2 arms<br>1. Immediate-release methylphenidate<br>2. Placebo<br>Six-month follow-up of study participants continuing methylphenidate treatment |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 34 (20 boys, 14 girls)<br>Number of participants randomly assigned: methylphenidate 22, placebo 12<br>Number of participants followed up: methylphenidate 22, placebo 12<br>Number of patients continuing methylphenidate treatment beyond the 1-day trial: 16<br>Number of participants followed up: 15<br>Number of withdrawals from extension trial: 1<br>**Regarding the group of patients participating in the 1-day trial**<br>Diagnosis of ADHD: DSM-IV-TR (combined (33.3%), hyperactive-impulsive (not stated), inattentive (50%), not otherwise specified (17.7%))<br>Age: mean 11.1 years (range 5 to 20)<br>IQ: mean: 81.4<br>Methylphenidate naive: 61.8%<br>Ethnicity: not stated<br>Country: Israel<br>Setting: hospital/out-patient clinic<br>Comorbidity in total sample: velocardiofacial syndrome (100%), oppositional defiant disorder (23.5%), specific phobia (26.5%), generalised anxiety disorder (11.8%), social phobia(11.8%), dysthymic disorder (8.8%) and separation anxiety (5.9%)<br>Comorbidity in methylphenidate group: congenital anomalies of the heart and great vessels (54.5%)<br>Comedication: no<br>Sociodemographics: not stated. The 2 groups had similar baseline demographics<br>**Inclusion criteria**<br>1. Not stated<br>**Exclusion criteria**<br>1. Not stated |
| Interventions | RCT: Participants were randomly assigned to methylphenidate or placebo<br>Mean methylphenidate dosage: 15.7 ± 5.6 mg (0.5 mg/kg)<br>Administration schedule: once<br>Duration of intervention: 1 day<br>Titration period: no mention, none<br>Washout before study initiation: 3 days<br>Treatment compliance: not stated<br>Follow-up: Some participants continued methylphenidate treatment beyond the RCT<br>Mean MPH dosage: not stated<br>Administration schedule: not stated<br>Duration of treatment: 6 months<br>Treatment compliance: 1 withdrew because of poor compliance |
| Outcomes | **Non-serious adverse events**<br>1. Cardiologic evaluation (ECG, heart rate and blood pressure): immediately before taking the pill (methylphenidate or placebo), and again after 90 minutes<br>2. Barkley Side Effects Rating Scale (modified Hebrew Version), parent-rated: 24 hours after methylphenidate administration and at 6-month follow-up |

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| **Notes** | Sample calculation: not stated<br>Ethics approval: Study protocol was approved by the Institutional Review Board of the Rabin Medical Center<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: no<br>**Comments from study authors**<br>1. We found that all participants (100%) with velocardiofacial syndrome treated with methylphenidate exhibited ≥ 1 side effect<br>2. Rate of all side effects immediately observed following initiation of treatment remained similarly high after 6 months of treatment<br>3. According to our findings, it seems that children with velocardiofacial syndrome did not develop tolerance to methylphenidate side effects<br>4. None of the children withdrew because of side effects<br>5. Limitations: short duration of parallel-group trial and relatively small sample size<br>**Key conclusions of study authors**<br>1. Use of methylphenidate in children with velocardiofacial syndrome appears to be effective and relatively safe<br>2. Comprehensive cardiovascular evaluation for children with velocardiofacial syndrome before and during stimulant treatment is recommended<br>Email correspondence with study authors: November 2013. We obtained supplemental information regarding ADHD diagnostic criteria from study authors. Furthermore, we received safety data from the study sample, excluding participants older than 18 years or with IQ < 70 (or both), but we decided not to use these data in our analyses, as data were missing for 60% of the control group |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | High risk | Participants were randomly assigned to drug or placebo in a 2:1 ratio, according to their order of recruitment |
| Allocation concealment (selection bias) | High risk | Participants were randomly assigned to drug or placebo in a 2:1 ratio, according to their order of recruitment |
| Blinding of participants and personnel (performance bias) | Low risk | Participants and their parents were blinded |
| Blinding of outcome assessment (detection bias) | Unclear risk | No information |
| Incomplete outcome data (attrition bias) | Low risk | No<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Low risk | Study authors have confirmed that planned outcomes for the 1-day (randomised controlled) trial were measured and reported |
| Vested interest bias | Low risk | This work was funded by the Basil O'Connor Starter Scholar Research Award of the March of Dimes, NARSAD (National Alliance for Research in Schizophrenia and Affective Disorders) Young Investigator Award, the Marguerite Stolz Award from the Sackler Faculty of Medicine and the National Institute on Drug Abuse (NIDA)<br>Conflicts of interest: Study authors have had no institutional or corporate/commercial relationships for the past 36 months that might pose a conflict of interest&& |

*Greenhill 2002*

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| **Methods** | Three-week, randomised, double-blind, 32-site, parallel trial with 2 arms<br>1. Modified-release methylphenidate<br>2. Placebo |
| **Participants** | Number of participants screened: 507<br>Number of participants included: 321<br>Number of participants randomly assigned: methylphenidate 158, placebo 163<br>Number of participants followed up: methylphenidate 141, placebo 135<br>Number of withdrawals: methylphenidate 17, placebo 28<br>Diagnosis of ADHD: DSM-IV (combined subtype or predominantly hyperactive-impulsive subtype)<br>Sex: 257 boys, 57 girls<br>Age: mean 9 years (range 6 to 15)<br>IQ: > 80<br>ADHD treatment naive: 36%<br>Ethnicity: Caucasian (71%), African American (15%), Hispanic (10%), other (4%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: none<br>Comedication: concomitant use of clonidine, anticonvulsant drugs and medications known to affect blood pressure and heart rate was not allowed<br>Sociodemographics: not stated. No significant differences in baseline demographics were noted between the 2 groups<br>**Inclusion criteria**<br>1. 6 to 16 years of age<br>2. Primary diagnosis of ADHD, combined subtype or predominantly hyperactive-impulsive subtype, as defined in DSM-IV<br>3. Did not respond to placebo with a reduction of ADHD symptoms during washout period<br>4. First-grade or higher school setting in which a single teacher could assess behaviour<br>5. Blood pressure, heart rate and oral temperature had to be within normal range<br>6. Did not respond to placebo with a reduction of ADHD symptoms during washout period<br>7. First-grade or higher school setting in which a single teacher could assess behaviour<br>8. Blood pressure, heart rate and oral temperature had to be within normal range<br>**Exclusion criteria**<br>1. Comorbid psychiatric diagnosis<br>2. History of seizure or tic disorder<br>3. Family history of Tourette's syndrome<br>4. IQ < 80<br>5. Inability to follow or understand study instructions<br>6. Female who had undergone menarche<br>7. Use of amphetamines, pemoline or an investigational drug within 30 days of study entry<br>8. Concomitant use of clonidine, anticonvulsant drugs or medications known to affect blood pressure, heart rate or CNS function<br>9. Hyperthyroidism or glaucoma<br>10. Concurrent chronic or acute illness (e.g. allergic rhinitis, severe cold) or disability that could confound study results<br>11. Failed a previous trial of stimulants for ADHD<br>12. Requiring a third daily dose in the afternoon or evening<br>13. Documented allergy or intolerance to methylphenidate<br>14. Living with anyone who currently had substance abuse disorder (excluding dependency) |

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| **Interventions** | Participants were randomly assigned to modified-release methylphenidate or placebo<br>Mean methylphenidate dosage: 40.7 mg/d (1.28 mg/kg/d)<br>Administration schedule: once daily<br>Duration of intervention: 3 weeks<br>Titration period: none<br>Treatment compliance: Medication counts showed satisfactory adherence in both groups |
| **Outcomes** | **General behaviour**<br>1. Conners' Teacher Global Index: rated twice daily (morning and afternoon), 3 times a week<br>2. Conners' Parent Global Index, 1 day of each weekend during the morning, afternoon and evening<br>**Non-serious adverse events**<br>1. Pittsburgh (11-item) Side Effects Questionnaire: parent- and teacher-rated weekly<br>2. Teachers completed a similar side effect questionnaire |
| **Notes** | Sample calculation: no<br>Ethics approval: yes; probably approved by an institutional review board<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; participants with a documented allergy or intolerance to methylphenidate were excluded<br>**Comments from study authors (limitations)**<br>1. Because no dose-response curves were collected on children in the study, we could not determine whether effects of modified-release methylphenidate were dose-related<br>2. Study inclusion and exclusion criteria were selected for milder cases of ADHD<br>3. Lower scores in this trial mean that findings may not be generalisable<br>4. Three-week duration of the trial did not allow investigators to determine whether dual-phase effects of modified-release methylphenidate persist with long-term treatment<br>5. Study design limited generalisability of the results because it excluded acute placebo responders and those who had failed to respond to any methylphenidate treatment before the start of the study<br>6. Parents were aware that researchers had the option of stepping up the "dose" of placebo each week<br>**Key conclusion of study authors**<br>1. Modified-release methylphenidate administered once daily in the morning was well tolerated and was significantly more effective in a double-blind comparison with placebo in controlling ADHD symptoms throughout the school day<br>Email correspondence with study authors: November and December 2013: not possible to get supplemental information regarding the study through personal email correspondence with study authors |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Stated "randomised". Stratification based on previous treatment before randomisation ensured equal distribution across the 2 treatment groups |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | Identical appearing modified-release methylphenidate and placebo capsules were packaged in blister cards |
| Blinding of outcome assessment (detection bias) | Unclear risk | Stated "double-blinded" |
| Incomplete outcome data (attrition bias) | Low risk | 316 were included in the safety population, and 314 in the ITT efficacy population. All statistical summaries and analyses were conducted for the ITT population using the LOCF approach for children who withdrew prematurely<br>Selection bias (e.g. titration after randomisation → exclusion): yes; exclusion of placebo responders |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. All pre-specified outcomes of interest have been reported |
| Vested interest bias | High risk | This study was funded by Celltech Pharmaceuticals Incorporated<br>Conflicts of interest: Dr. Greenhill is a consultant for Celltech-Medeva and a member of its medical advisory board. Drs. Findling and Swanson are consultants for Celltech-Medeva |

*Greenhill 2006*

| Methods | Seven-week multi-centre, randomised, double-blind, placebo-controlled, parallel trial with 2 arms<br>1. Extended-release dexmethylphenidate<br>2. Placebo<br>To compare the efficacy and safety of extended-release dexmethylphenidate vs placebo in paediatric patients with ADHD<br>Pre-randomisation phase of up to 2 weeks followed by double-blind treatment phase for 7 weeks (5 weeks of dose titration followed by 1 week of optimal constant dose) |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 103<br>Number of participants randomly assigned: methylphenidate 53, placebo 50<br>Number of participants followed up: methylphenidate 48, placebo 37 (ITT analyses: methylphenidate 52, placebo 45)<br>Number of withdrawals: methylphenidate 5, placebo 13<br>Diagnosis of ADHD: DSM-IV, extended-release dexmethylphenidate (combined (83%), hyperactive-impulsive (1.9%), inattentive (15.1%))<br>Age: mean methylphenidate 9.6 years, placebo 10.4 years (range 6 to 17)<br>IQ: > 70 (age-appropriate functioning levels academically)<br>Sex: 66 boys, 37 girls<br>Methylphenidate naive: 40<br>Ethnicity: Caucasian (60%), African American (23.3%), other (16.5%)<br>Country: USA<br>Setting: classroom setting<br>Comorbidity: no psychiatric comorbidity<br>Comedication: not stated<br>Sociodemographics: not stated. No significant difference in baseline demographics was noted between the 2 groups. See Tables 1 and 2<br>**Inclusion criteria**<br>1. ADHD diagnosis as per DSM-IV<br>2. Baseline age of 6 to 17 years<br>3. Conners' ADHD/DSM-IV Scales - Teacher, for boys 6 to 8 years ≥ 27, 9 to 11 years ≥ 24, 12 to 14 years ≥ 19, 15 to 17 years ≥ 14<br>4. Conners' ADHD/DSM-IV Scales - Teacher, for girls 6 to 8 years ≥ 16, 9 to 11 years ≥ 13, 12 to 14 years ≥ 12; 15 to 17 years ≥ 6<br>5. Age-appropriate functioning levels academically<br>6. Negative pregnancy test and adequate contraception<br>**Exclusion criteria**<br>1. Clinically significant abnormalities in vital signs, physical examination findings or laboratory test results<br>2. History of seizures or use of anticonvulsant medication<br>3. Comorbid psychiatric conditions (obtained by clinical interview)<br>4. Any medical condition that could interfere with study participation or assessments, or that may pose danger with administration of methylphenidate<br>5. Psychotropic medications<br>6. Initiation of psychotherapy within the past 3 months<br>7. Positive urine drug screen<br>8. History of poor response or intolerance to methylphenidate<br>9. Pregnant or nursing<br>10. Any other investigational drug within 30 days of study entry |
| Interventions | Participants were randomly assigned to an extended-release formulation of dexmethylphenidate or placebo. Permitted doses were 5 mg/d for the first week; 5 or 10 mg/d for the second week; 5 mg/d, 10 mg/d or 15 mg/d for the third week; 5 mg/d, 10 mg/d, 15 mg/d or 20 mg/d for the fourth week; and 5 mg/d, 10 mg/d, 15 mg/d, 20 mg/d or 30 mg/d for the fifth through seventh weeks<br>Mean final methylphenidate dosage: 24.0 ± 7.1 mg/d<br>Administration schedule: once daily in the mornings<br>Duration of intervention: 5-week titration period plus 2 weeks at a constant dose<br>Titration period: initiated after randomisation<br>Treatment compliance: At each study visit, compliance was assessed by investigator and study staff on the basis of pill count and participant report |

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| Outcomes | **ADHD symptoms**<br>1. Conners' ADHD/DSM-IV Scales - Teacher: rated weekly by teachers<br>2. Conners' ADHD/DSM-IV Scales - Parent: rated weekly by parents<br>**Quality of life**<br>1. Child Health Questionnaire, Parent Form 50: parent-rated at final visit<br>**Serious adverse events**<br>1. Spontaneous reporting recorded weekly: no deaths or serious adverse events<br>**Non-serious adverse events**<br>1. Vital signs were rated weekly<br>2. Spontaneously reported adverse events were recorded weekly |
| Notes | Sample calculation: Assumptions for sample size and power included treatment difference of 9.0 and and SD of 13.5<br>Ethics approval: no information provided<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; participants with history of poor response or intolerance to methylphenidate were excluded<br>Withdrawals due to adverse events: methylphenidate 0, placebo 1<br>**Comments from study authors**<br>1. It is of interest that no participant who received extended-release dexmethylphenidate discontinued the study because of an adverse event. This may result in part from the fact that more than one-third of participants in each treatment group had prior experience with ADHD medications (mainly methylphenidate and dexmethylphenidate) and in part from the flexible-dose design of the study<br>2. Another possible limitation is that patients with previous methylphenidate or dexmethylphenidate experience were enrolled only if they had not experienced moderate to severe adverse reactions. By excluding patients who could not tolerate methylphenidate or dexmethylphenidate, investigators may have inflated the apparent safety and tolerability of extended-release dexmethylphenidate. However, only about one-fourth of the participants in each treatment group had prior experience with methylphenidate or dexmethylphenidate, so this factor probably had little impact on adverse event rates during the study<br>**Key conclusions of study authors**<br>1. In conclusion, results of this trial indicate that extended-release dexmethylphenidate administered once daily in doses of 5 mg to 30 mg is safe and effective for treatment of paediatric patients with ADHD symptoms, as reflected by its significant superiority over placebo on Conners' ADHD/DSM-IV Scales - Teacher, Conners' ADHD/DSM-IV Scales - Parent, Clinical Global Impressions - Improvement Scale and Clinical Global Impressions - Severity Scale, and in the Child Health Questionnaire Psychosocial Component score<br>2. Extended-release dexmethylphenidate was well tolerated and had a safety profile consistent with those of other methylphenidate and dexmethylphenidate formulations, resulting in appetite reduction and reduced weight in some patients<br>**Comments from review authors**<br>1. Statistically significant treatment by centre interaction in primary efficacy analysis<br>2. Study authors defined baseline scores on Conners' ADHD/DSM-IV Scales - Teacher (to be included) as different scores for different age groups, but they informed efficacy as the difference from baseline to endpoint in all medicated individuals<br>3. As precise information on dose (mg/kg/d) was lacking, it is difficult to evaluate whether 24 mg/d was enough for participants in this age range (6 to 17 years)<br>Email correspondence: July 2014. Wrote to Novartis to request additional information but have not received a reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomised, no further description provided |
| Allocation concealment (selection bias) | Unclear risk | No description provided |
| Blinding of participants and personnel (performance bias) | Unclear risk | Double-blind, no further description provided |
| Blinding of outcome assessment (detection bias) | Unclear risk | Double-blind, no further description provided |
| Incomplete outcome data (attrition bias) | Low risk | Study used an ITT analysis. LOCF analysis was used to impute missing values for all final visit analyses<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | High risk | Study authors defined baseline scores on Conners' ADHD/DSM-IV Scales - teacher-rated, as inclusion criteria (different scores for age groups), but they informed efficacy as the difference from baseline to endpoint for all medicated individuals |
| Vested interest bias | High risk | Study funded by Novartis<br>Conflicts of interest: Two study authors are employed by Novartis. Only Roberta R. Ball has no conflicts of interest |

### *Grizenko 2012*

| Methods | Double-blind, cross-over, placebo-controlled, 2-week trial of methylphenidate in children diagnosed with ADHD<br>1. Methylphenidate (0.5 mg/kg, b.i.d.)<br>2. Placebo<br>Phases: 2 |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 430 (average IQ group). Participants were randomly assigned to 1 of 2 possible drug condition orders<br>Number of participants followed up: 430 (334 boys, 96 girls)<br>Number of withdrawals: not stated<br>Diagnosis of ADHD: DSM-IV (combined 96 (48.73%), hyperactive-impulsive not stated for average IQ group alone, inattentive not stated for average IQ group alone)<br>Age: mean 9.45 years (range 6 to 12)<br>IQ: mean 96.68 ± 9.98 (range 80 to 120)<br>Methylphenidate naive: not stated for average IQ group alone<br>Ethnicity: not stated<br>Country: Canada<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: income group 4.62 (SD 1.56). Income groups set at 1 (< Can$ 6000), 2 (Can$ 6000 to 10,000), 3 (Can$ 10,000 to 20,000), 4 (Can$ 20,000 to 30,000), 5 (Can$ 30,000 to 40,000) and 6 (> Can$ 40,000)<br>**Inclusion criteria**<br>1. Children 6 to 12 years of age<br>2. Diagnosed with ADHD by a psychiatrist or a paediatrician participating in a double-blind, placebo-controlled trial. Children were recruited from the Disruptive Behavior Disorders Program and from the general sector out-patient clinic at Douglas Hospital in Montreal, a psychiatric university teaching hospital<br>**Exclusion criteria**<br>1. Children with IQ < 70 (as measured by the Wechsler Intelligence Scale for Children)<br>2. Met DSM-IV criteria for psychosis, pervasive developmental disorder or Tourette's syndrome<br>3. Previous intolerance or allergic reaction to methylphenidate (Grizenko 2006 and Grizenko 2012 - both in Grizenko 2012) |
| Interventions | Participants were randomly assigned to 1 of 2 possible drug condition orders of methylphenidate and placebo<br>Mean methylphenidate dosage: 0.5 mg/kg/d<br>Administration schedule: b.i.d. morning and noon<br>Duration of each medication condition: methylphenidate 1 week, placebo 1 week (including weekends)<br>Washout before study initiation: 1 week before the start of the trial<br>Medication-free period between interventions: not stated, appears to have been none<br>Titration period: none<br>Treatment compliance: not stated |

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| Outcomes | **ADHD symptoms**<br>1. Conners' Global Index - Teacher Version: once a week + 1 week before medication trial<br>2. Conners' Global Index - Parent Version: once a week (1 week before medication trial and on the Sunday after children were given their medication of the weekend (Grizenko 2006 - in Grizenko 2012)<br>**General behaviour**<br>1. Parents completed a Child Behavior Checklist 1 week before the start of the medication trial<br>**Serious adverse events**<br>1. No important adverse events or side effects were noted<br>**Non-serious adverse events**<br>1. Barkley Side Effects Rating Scale |
| Notes | Sample calculation: not stated<br>Ethics approval: yes<br>**Key conclusion of study authors**<br>1. Grizenko 2012: All children with ADHD within normal and high levels of intellectual functioning respond equally to psychostimulant treatment; proper medication management is necessary for all children with the disorder<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes (see summary of participants)<br>Any withdrawals due to adverse events: not stated<br>Email correspondence with study authors: October 2013. We received some data from study authors. We sent another email to ask for additional information but have not received a response |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomisation was completed by a research psychologist who had no contact with participants |
| Allocation concealment (selection bias) | Low risk | "The sealed envelope containing the information about the order of MPH and placebo administration for the participant was opened after the CCR rating was assigned and recorded" |
| Blinding of participants and personnel (performance bias) | Low risk | "Both drug and placebo were prepared by a pharmacist in identical coloured gelatine capsules" |
| Blinding of outcome assessment (detection bias) | Low risk | See above |
| Incomplete outcome data (attrition bias) | Low risk | No<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Low risk | Estimated enrolment: 700<br>Study start date: November 1999<br>Estimated primary completion date: March 2018 (final data collection date for primary outcome measure) |
| Vested interest bias | Unclear risk | Study was supported by the Canadian Institutes of Health<br>Conflicts of interest: Dr. Joober has received consultation honoraria from Pfizer Canada and Janssen Ortho. Dr. Zappitelli receives research salary support and grant funding from the Kidney Research Scientist Core Education and National Training Programme, the Fondation de Recherche en Sante du Quebec and the Research Institute of the McGill University Health Centre, for research not related to this manuscript |

*Gruber 2007*

| Methods | Fourteen-day, double-blind, placebo-controlled, cross-over study with 2 interventions<br>1. Placebo<br>2. Methylphenidate |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 37 (31 boys, 6 girls). Participants were randomly assigned to 1 of 2 possible drug condition orders<br>Number of participants followed up: 37<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-IV (combined (70%), hyperactive-impulsive (11%), inattentive (19%))<br>Age: mean 9.2 years (range 6 to 12)<br>IQ: mean 96.7<br>Methylphenidate naive: not stated<br>Ethnicity: Caucasian (94%), other (6%)<br>Country: Canada<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder (30%), conduct disorder (46%), major depressive disorder (5%), general anxiety disorder (3%)<br>Comedication: no<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. ADHD according to DSM-IV<br>2. Patient at the Disruptive Behavior Disorders Program and in the out-patient department of Douglas Mental Health University Institute in Montreal<br>3. Between 6 and 12 years of age<br>**Exclusion criteria**<br>1. Score < 80 on the Wechsler Intelligence Scale for Children, Third Edition<br>2. Diagnosis of psychosis<br>3. Diagnosis of Tourette's syndrome<br>4. Pervasive developmental disorder<br>5. Taking any medication other than methylphenidate<br>6. Previous intolerance/allergic reaction to any psychostimulant |
| Interventions | Participants were randomly assigned to 1 of 2 possible drug condition orders of methylphenidate and placebo<br>Mean methylphenidate dosage: 0.5 mg/kg/d<br>Administration schedule: twice daily, morning and noon<br>Duration of each medication condition: 7 days<br>Washout before study initiation: no<br>Medication-free period between interventions: no<br>Titration period: none<br>Treatment compliance: not stated |
| Outcomes | **General behaviour**<br>• Child Behavior Checklist, daily<br>**Non-serious adverse events**<br>• Sleep assessment using miniature antigraphs, measured daily |

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| **Notes** | Ethics approval: Study was approved by the Research Ethics Board of Douglas Mental Health University Institute<br>**Key conclusion of study authors**<br>1. Findings of the present study support the hypothesis that sleep moderates performance on the Continuous Performance Test in children with ADHD receiving placebo or methylphenidate<br>**Comment from review authors**<br>1. Unfortunately, the data are not useable because of how the study is set up<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes (see exclusion criteria)<br>Any withdrawals due to adverse events: no<br>Email correspondence with study authors: February and March 2014. Emailed study author twice but have not received a reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Order of administration (methylphenidate or placebo) was determined by random assignment |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | "MPH and placebo were prepared in identical coloured gelatin capsules by the hospital's clinical pharmacist, who was not involved in the study in any other way. Capsules were sealed in individual, daily-dose envelopes to help control accurate administration" |
| Blinding of outcome assessment (detection bias) | Unclear risk | No information |
| Incomplete outcome data (attrition bias) | High risk | Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): yes |
| Selective reporting (reporting bias) | Unclear risk | No information |
| Vested interest bias | Low risk | This was not an industry-supported study<br>Conflicts of interest: Study authors have indicated no financial conflicts of interest |

### *Hale 2011*

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| **Methods** | Cross-over trial with 2 interventions<br>1. Methylphenidate<br>2. Placebo<br>Phases: baseline, placebo, low-dose methylphenidate and high-dose methylphenidate for 4 weeks per medication phase |

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| Participants | Number of participants screened: 65<br>Number of participants included: 56 (39 boys, 17 girls). Participants were randomly assigned to 1 of 6 possible drug condition orders<br>Number of participants followed up: not stated<br>Number of withdrawals: not stated<br>Diagnosis of ADHD: DSM-IV-TR (combined (58.9%), hyperactive-impulsive (7.1%), inattentive (33.9%))<br>Age: mean 120.84 months (SD 30.85 months, range 6 to 16 years)<br>IQ: mean 99.56 (SD 6.84, n = 41)<br>Methylphenidate naive: number not stated ("All participants were either medication naive or received and appropriate wash-out period")<br>Ethnicity: European American (82%), African American (18%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: specific learning disability (n = 13), oppositional defiant disorder/conduct disorder (n = 11), anxiety/depression (n = 6)<br>Comedication: not stated<br>Sociodemographics: middle class (n = 44), lower class (n = 12); urban (n = 36), suburban (n = 13), rural (n = 7)<br>**Inclusion criteria**<br>1. Diagnosis based on DSM-IV-TR criteria by referring physician - independent confirmation by licensed and/or certified psychologist<br>2. Demonstrated significant attention, hyperactivity and/or impulse control problems interfering with major life function in both home and school settings<br>3. ≥ 1.5 SD above the mean on ≥ 1 of the attention problems on the Child Behavior Checklist, Teacher Report Form; Inattention and/or Hyperactive-Impulsive subscales of the Conners' Parent Rating Scale - Revised and Long; or Conners' Teacher Rating Scale - Revised<br>**Exclusion criteria**<br>1. ≥ 1 comorbid secondary diagnosis<br>2. History of mental retardation<br>3. Seizure disorder - brain injury<br>4. Other medical condition affecting cognitive or neuropsychological performance - missing or different instruments for measuring methylphenidate response (i.e. missing data) |
| Interventions | Participants were randomly assigned to 1 of 6 possible drug condition orders of methylphenidate (0.15 mg/kg, 0.30 mg/kg) and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: twice daily<br>Duration of each medication condition: 4 weeks<br>Washout before study initiation: 2 days<br>Medication-free period between interventions: no<br>Titration period: none<br>Treatment compliance: not stated |

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| Outcomes | **ADHD symptoms**<br>1. Conners' Teacher Rating Scale - Revised and Long: teacher-rated at baseline and at treatment follow-up<br>**General behaviour**<br>1. Schools Situation Questionnaire - Revised: teacher-rated at baseline and at treatment follow-up<br>**Non-serious adverse events**<br>1. Side Effects Rating Scale, unclear who rated: at baseline and at treatment follow-up |
| Notes | Sample calculation: no<br>Ethics approval: not stated<br>**Comment from study authors**<br>1. Several study limitations are worth noting. First. age limitations. Second, neuropsychological tests that were not counterbalanced and analysed for order effects. Third, inter-rater reliability during methylphenidate trials. Fourth, intelligence/cognitive screening<br>**Key conclusion of study authors**<br>1. Robust cognitive and behavioural methylphenidate response was achieved for children with significant baseline executive working memory/self regulation (EWM/SR) impairment, yet response was poor for those with adequate EWM/SR baseline performance. Even for strong methylphenidate responders, the best dose for neuropsychological functioning was typically lower than the best dose for behaviour. Findings offer 1 possible explanation for why long-term academic methylphenidate treatment gains in ADHD have not been realised<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: June to August 2014. Emailed study authors twice to request additional information but have not received a reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | All medications and placebos were prepared by the study pharmacist, who randomly assigned children to 1 of 6 trial orders in placebo (P), low-dose (L) and high-dose (H) conditions (P-L-H, P-H-L, L-P-H, L-H-P, H-L-P, H-P-L) |
| Allocation concealment (selection bias) | Low risk | Research assistants, teacher, parents and participants were blinded to the order of conditions. Ground methylphenidate tablet was placed in lactose-filled opaque capsules for active drug conditions, with lactose included only for the placebo condition, and was administered twice per day |
| Blinding of participants and personnel (performance bias) | Low risk | Research assistants, teacher, parents and participants were blinded to the order of conditions. All medications and placebos were prepared by the study pharmacist. Ground methylphenidate tablet was placed in lactose-filled opaque capsules for the active drug condition, with lactose included only for the placebo condition |
| Blinding of outcome assessment (detection bias) | Low risk | After results were analysed, the order of conditions was revealed |
| Incomplete outcome data (attrition bias) | High risk | Participants for whom data were missing or different instruments were used for methylphenidate response were excluded |
| Selective reporting (reporting bias) | Unclear risk | No protocol identified |
| Vested interest bias | Low risk | Research part funded by the Neuropsychiatric Research Institute, Fargo, North Dakota, USA<br>Conflicts of interest: Study authors disclose no conflicts of interest |

*Heriot 2008*

| Methods | Three-month, parallel trial with 4 arms<br>1. Methylphenidate and parent training programme<br>2. Methylphenidate and supportive non-training parent group<br>3. Placebo and parent training<br>4. Placebo and supportive non-training parent group |
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| Participants | Number of participants screened: 93<br>Number of participants included: 20 to 26 (NB: 6 withdrew, but unclear whether before or after random assignment)<br>Number of participants randomly assigned: not stated<br>Number of participants followed up: methylphenidate + parent training 4, methylphenidate + no training 4, placebo + training 4, placebo + no training 4<br>Number of withdrawals: not stated<br>Sex: 13 boys, 3 girls<br>Diagnosis of ADHD: DSM-IV (combined (25%), hyperactive-impulsive (56%), inattentive (19%))<br>Age: mean 4.78 years (range 3 to 6)<br>IQ: mean 97 (range 80 to 123)<br>Methylphenidate naive: 100%<br>Ethnicity: no information<br>Country: New Zealand<br>Setting: out-patient clinic<br>Comorbidity (type: ODD 5/31%)<br>Comedication: no<br>Sociodemographics: SES group 1: 1, group 2: 0, group 3: 3, group 4: 4, group 5: 3, group 6: 5. No significant differences in baseline demographics were noted between the 2 groups<br>**Inclusion criteria**<br>1. Between 3.0 and 5.9 years of age<br>2. Resident with a primary caregiver for ≥ 6 months<br>3. Meet diagnostic criteria for ADHD as defined in DSM-IV<br>4. Features of ADHD had to be present for ≥ 12 months and to a degree that was considered to be developmentally inappropriate and functionally inappropriate and functionally impairing across settings<br>5. Above the 93rd percentile on the Global Index subscale of the Conners' Rating Scales<br>**Exclusion criteria**<br>1. Currently in hospital<br>2. Currently in another treatment study<br>3. Currently receiving treatment<br>4. Full scale IQ < 80<br>5. Pervasive developmental disorder or psychosis<br>6. Major neurological or medical illness that would interfere with participation or require medications incompatible with methylphenidate<br>7. Chronic serious tics or Tourette's disorder<br>8. History of child abuse<br>9. Inability of parent to understand English |
| Interventions | Participants were randomly assigned to methylphenidate + parent training, methylphenidate + no parent training, placebo + parent training or placebo + no parent training<br>Mean methylphenidate dosage: 0.3 mg/kg<br>Administration schedule: twice a day - morning and lunchtime<br>Duration of intervention: 3 months<br>Titration period: Dosage was built up over the first week<br>Treatment compliance: not stated |

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| Outcomes | **ADHD symptoms**<br>1. ADHD Rating Scale-IV Parent and Teacher Versions: data not reported in an useable form - not possible to obtain data from study author<br>2. Conners' Parent Rating Scale - Revised, Long Version: no data provided in the article<br>3. Conners' Teacher Rating Scale - Revised, Long Version: no data provided in the article<br>**Non-serious adverse events**<br>1. Stimulant drug, Barkley Side Effects Rating Scale |
| Notes | Sample calculation: no<br>Ethics approval: yes; obtained from the University of Waikato, Department of Psychology Ethical Review Committee and the Waikato Ethics Committee for Waikato Hospital<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Comments from study authors**<br>1. Seven of the 16 children no longer met DSM-IV (1994) diagnostic criteria for ADHD at the end of the study<br>2. Ethnicity did not appear to affect outcomes, although it was unclear whether the content of the programme was equally appropriate for all ethnic groups<br>3. Limitations<br>a. Small number of participants<br>b. Of those willing to participate, only 43% met eligibility criteria for the study<br>c. No follow-up data<br>**Key conclusion of study authors**<br>1. Children were more likely to improve when treatment involved ≥ 1 active component (medication or parent training). However, variability in individual parental and child participant responses to all treatment conditions was notable, indicating the importance of interaction between treatment variables and other factors. Findings are discussed within the framework of a transactional model, and inferences are drawn about limitations of the idea that a "best treatment" exists that is universally applicable. Although improvement among children receiving treatment with methylphenidate was greater than for others, it is notable that all treatments were associated with improvement in some children<br>Email correspondence with study authors: January, February and May 2014. Emailed study author but have not received a reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | High risk | Participants were allocated to conditions sequentially, using RAND function (SPSS) to generate the sequence. Each parent was randomly assigned to attend the training programme group or the support group. |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Low risk | Throughout the period of data collection, participants and therapist were blinded to medication status |
| Blinding of outcome assessment (detection bias) | Low risk | Throughout the period of data collection, participants and therapist were blinded to medication status. All parents and teachers were blinded to the intervention |
| Incomplete outcome data (attrition bias) | High risk | Only data for completing participants were reported<br>Selection bias (e.g. titration after randomisation → exclusion): unclear. Four were excluded after randomisation because of "treatment integrity problems" |
| Selective reporting (reporting bias) | Unclear risk | We were unable to identify a protocol |
| Vested interest bias | Low risk | No funding to conduct the study was received from any party<br>Conflicts of interest: None of the study authors are affiliated with pharmaceutical companies |

### *Hicks 1985*

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| **Methods** | Double-blind, cross-over trial with 2 interventions<br>1. Methylphenidate, low and high doses<br>2. Placebo |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 44. Participants were randomly assigned to different low and high doses of methylphenidate and to placebo<br>Number of participants followed up: 44 (36 boys, 8 girls; 20 in-patients, 24 out-patients)<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-III (subtype not stated)<br>Age: mean 8.4 years (SD 1.75, range not reported)<br>IQ: mean 98.31 (SD 12.96)<br>Methylphenidate naive: not stated<br>Ethnicity: Caucasian (68.2%), African American (31.8%)<br>Country: not stated<br>Setting: out-patient clinic and patient ward<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: mean 3.59 (SD 1.29) (Hollingshead 2-factor SES index)<br>**Inclusion criteria**<br>1. Diagnosis of ADHD according to DSM-III<br>**Exclusion criteria**<br>1. None stated |

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| Interventions | Participants were randomly assigned to different orders of methylphenidate (low-dose 0.3 mg/kg, high-dose 0.6 mg/kg) and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: b.i.d. morning and noon<br>Duration of each medication condition: 12 for in-patients, 19 for out-patients<br>Washout before study initiation: not stated<br>Medication-free period between interventions: 68 hours<br>Titration period: none<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. Conners' Parent Rating Scale: rated weekly<br>2. Conners' Teachers Rating Scale: rated weekly<br>**Non-serious adverse events**<br>1. Pulse, measured once in each treatment condition, before and 1 hour after treatment<br>2. Blood pressure, measured once in each treatment condition, before and 1 hour after treatment<br>3. Blood samples, measured once in each treatment condition, before and 1 hour after treatment, including growth hormone, prolactin, thyroid-stimulating hormone |
| Notes | Sample calculation: not stated<br>Ethics approval: yes<br>**Key conclusion of study authors**<br>1. "MPH appears able to engage homeostatic mechanisms which take over and operate to return functioning to a more normal level"<br>**Comment from review authors**<br>1. Study participants are both in-patients and out-patients; therefore the sample group is highly heterogeneous<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: no<br>Email correspondence with study authors: March 2014. We obtained from study authors supplemental information regarding funding and ethics. Not able to obtain additional data as they are no longer available |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not stated |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Unclear risk | Double-blind |
| Blinding of outcome assessment (detection bias) | Unclear risk | Double-blind |
| Incomplete outcome data (attrition bias) | Unclear risk | Not stated |
| Selective reporting (reporting bias) | Unclear risk | No protocol available |
| Vested interest bias | Low risk | Funded by the National Institutes of Health (NIH)<br>Conflicts of interest: not stated |

### *Hoeppner 1997*

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| **Methods** | Double-blind, cross-over trial with 2 interventions<br>1. High-dose (H) methylphenidate<br>2. Low-dose (L) methylphenidate<br>3. Placebo (P)<br>Four orders<br>1. P, L, H<br>2. H, P , L<br>3. P, H, L<br>4. L, P, H |
| **Participants** | Number of participants screened: 95<br>Number of participants included: 50. Participants were randomly assigned to different orders of low-dose and high-dose methylphenidate and placebo<br>Number of participants followed up: 50 (39 boys, 11 girls)<br>Number of withdrawals: none<br>Diagnosis of ADHD: DSM-III-R<br>Age: mean 9.6 years (range 6 to 18.1)<br>IQ: not stated<br>Methylphenidate naive: not stated<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Meeting DSM-III-R ADHD, DSM-III ADD or DSM-III-ADD/H criteria<br>2. Score ≥ 1½ SD above the norm on the Conners' Parent Rating Scale or the Conners' Teacher Rating Scale<br>**Exclusion criteria**<br>1. No information |

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| Interventions | Participants were randomly assigned to different possible orders of high-dose methylphenidate (0.3 mg/kg), low-dose methylphenidate (0.15 mg/kg) and placebo (doses rounded up to the nearest 2.5 mg)<br>Mean methylphenidate dosage: no information<br>Administration schedule: twice a day - 8:00 AM and 12:00 PM<br>Duration of each medication condition: 1 week<br>Washout before study initiation: "received an appropriate wash-out period"<br>Medication-free period between interventions: from lunchtime until next morning - 20 hours<br>Titration period: none<br>Treatment compliance: no information |
| Outcomes | **ADHD symptoms**<br>1. Conners' Parent/Teacher Rating Scale: completed daily |
| Notes | Sample calculation: no<br>Ethics approval: no information<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Comments from study authors**<br>1. Dependent measures in this study often failed to detect significant dose-response effects when analysed individually, and placebo effect were found for 4 of the 9 measures. Although ratings from the Conners' Parent and Teacher Rating Scales were sensitive to dose-response effects, findings were not uniform across raters and did not correspond with cognitive response<br>2. Small sample size<br>**Key conclusion of study authors**<br>1. According to cognitive rank order ratings, linear and quadratic methylphenidate response patterns were identified, with the best dose for each group significantly different from that obtained for all other conditions<br>Email correspondence with study authors: March 2014. Emailed study authors to request additional information but have received no reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No information |
| Allocation concealment (selection bias) | Low risk | Pharmacists randomly assigned participants to 1 of 4 trial sequences |
| Blinding of participants and personnel (performance bias) | Low risk | Placebo consisted of an opaque capsule filled with lactose; active drug consisted of the same lactose-filled capsule, to which methylphenidate was added |
| Blinding of outcome assessment (detection bias) | Low risk | Placebo consisted of an opaque capsule filled with lactose; active drug consisted of the same lactose-filled capsule, to which methylphenidate was added |
| Incomplete outcome data (attrition bias) | Low risk | No drop-outs<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Low risk | No reporting bias |
| Vested interest bias | Unclear risk | No information |

*Horn 1991*

| Methods | Twelve-week, double-blind, randomised, parallel trial with 6 arms<br>1. Placebo<br>2. Low-dose methylphenidate<br>3. High-dose methylphenidate<br>4. Placebo + behavioural parent training + child self control instruction<br>5. Low-dose methylphenidate + behavioural parent training + child self control instruction<br>6. High-dose methylphenidate + behavioural parent training + child self control instruction.<br>Nine-month follow-up |
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| **Participants** | Number of participants screened: 117<br>Number of participants included: 107 (83 boys, 24 girls)<br>Number of participants randomly assigned: 16 to each arm<br>Number of withdrawals after randomisation: 18<br>Number followed up: at end of study (12 weeks) 78, 9 months after termination of study 71<br>Diagnosis of ADHD: DSM-III-R (subtype not stated)<br>Age: mean 8.27 years (range 7 to 11)<br>IQ: > 70<br>Methylphenidate naive: not stated<br>Ethnicity: Caucasian (84.9%), African American (9.4%), Hispanic (3.8%), Asian American (1.9%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: conduct disorder (7.5%), disruptive oppositional disorder (15%), oppositional defiant disorder (43%)<br>Comedication: not stated<br>Sociodemographics: mean yearly family income USD $25,019. No significant differences in baseline demographics were noted between treatment groups or between treatment groups and treatment drop-outs in any of the following parameters: child's age, grade, sex, IQ; parental marital status, annual family income and maternal education and age. However, a significantly greater number of non-white children were included in the placebo alone condition than in remaining treatment conditions or among treatments drop-outs<br>**Inclusion criteria**<br>1. 7 to 11 years of age<br>2. Exact agreement between a licensed clinical psychologist and a board certified paediatrician with respect to diagnosis of ADHD according to DSM-III-R criteria<br>3. Score on Hyperkinesis Index of the Conners' Parent or Teacher Rating Scale ≥ 2 SD above published means<br>4. Current psychostimulant therapy required to be withdrawn for the course of the study<br>**Exclusion criteria**<br>1. Comorbid anxiety, depressive disorder or both<br>2. Gross physical impairments, intellectual deficits or psychosis in child or parents |
| **Interventions** | Washout before study initiation: 2 weeks before initial diagnostic evaluation<br>Participants were randomly assigned to 1 of 6 treatment conditions, including placebo, low-dose methylphenidate (0.4 mg/kg) and high-dose methylphenidate (0.8 mg/kg)<br>Administration schedule: daily<br>Duration of intervention: 12 weeks<br>Titration period: no<br>Treatment compliance: 87.39% of parents in the non-placebo medication conditions group reported anonymously that their child took the medications almost every day, whereas the remainder of families reported usage an average of 3 to 4 days a week. Stimulant medication was withdrawn immediately after post-test assessments<br>Follow-up: 9 months |

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| **Outcomes** | **ADHD symptoms**<br>All dependent measures were administered at pre-test, post-test (within 1 week or 2 weeks of the end of the treatment phase of the study) and follow-up<br>1. Child Behaviour Checklist<br>2. Swanson, Nolan and Pehlam Scale<br>3. Conners' Parent Rating Scale<br>4. Conners' Teacher Rating Scale<br>**Adverse events**<br>1. Medication side effects, monitored by a board certified paediatrician |
| **Notes** | Sample calculation: no information<br>Ethics approval: no information<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: August 2013. Not possible to receive supplemental information or data through personal email correspondence with study authors. They do not recommend inclusion of the study in this review because of problems with the design and methods used at the time the study was carried out ( Ramstad 2013a [pers comm]) |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Two of 12 families were randomly assigned to each of the 6 treatment conditions. This procedure was repeated 8 times, so that by the end of the study, 16 families were randomly assigned to each of the 6 treatment conditions, for a total of 96 families |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | Double-blind |
| Blinding of outcome assessment (detection bias) | Low risk | Double-blind. Note that assessors were blinded to treatment status at all times |
| Incomplete outcome data (attrition bias) | Low risk | Analyses were conducted on 4 samples: (1) participants completing the entire study and followed up at 9 months (n = 71), (2) participants completing the entire study (n = 78), (3) participants completing the entire study + participants completing ≥ 6 weeks (n = 90) and (4) all of the above + those who dropped out immediately after initiating treatment (n = 96). When no post-test and/or follow-up data were available for drop-outs, pre-test values or post-test values, or both, were substituted. Given that analyses produced essentially the same results, only the analyses that include completers are reported<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | No protocol |
| Vested interest bias | Unclear risk | No information |

## *Ialongo 1994*

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| **Methods** | Fourteen-week, parallel trial with 3 arms<br>1. Placebo<br>2. Low-dose stimulant therapy<br>3. High-dose stimulant therapy |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 48 (35 boys, 13 girls). 16 children randomly assigned to each of the following 3 treatment conditions: (1) medication placebo alone, (2) low-dose (0.4 mg/kg) stimulant therapy, or (3) high-dose (0.8 mg/kg) stimulant therapy. A sample of 21 non-clinical controls (13 boys and 8 girls) was also included in the study<br>Number of withdrawals: Seven families dropped out from pre-test to post-test: high-dose methylphenidate 3, placebo 4<br>Numper of participants followed up: low-dose methylphenidate 16, high-dose methylphenidate 13, placebo 12<br>Diagnosis of ADHD: DSM-III-R (subtype not stated)<br>Age: mean 7.97 years (SD 1.4, range 7 to 11)<br>IQ: ≤ 70<br>Methylphenidate naive: 98%<br>Ethnicity: Caucasian (78.0%), African American (12.2%), Hispanic (9.8%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: conduct disorder (n = 5), oppositional defiant disorder (n = 12)<br>Comedication: no<br>Sociodemographics: middle-income families. No significant differences between treatment groups or between treatment groups and drop-outs in any participant and/or demographic characteristics at pre-test, with the exception of ethnicity. A significantly greater proportion of African American children were included in the placebo condition than in the high-dose condition<br>**Inclusion criteria**<br>1. Diagnosis of ADHD according to DSM-III-R<br>2. Exact agreement between 2 assessors (paediatrician and psychologist) with respect to ADHD diagnosis<br>3. Score on Hyperkinesis Indices of the Conners' Parent and Teacher Rating Scale ≥ 2 SD above published means<br>**Exclusion criteria**<br>1. Comorbid anxiety and/or depressive disorder<br>2. Gross physical impairment<br>3. Intellectual deficits<br>4. Psychosis in child or parents<br>5. IQ < 70 (measured with the Peabody Picture Vocabulary Test - Revised) |
| **Interventions** | Participants were randomly assigned to 3 treatment conditions: (1) medication placebo alone, (2) low-dose (0.4 mg/kg) stimulant therapy or (3) high-dose (0.8 mg/kg) stimulant therapy<br>Duration of intervention: 14 weeks<br>Titration period: no<br>Treatment compliance: One check on medication compliance consisted of periodic dispensing of medication over the course of the study during follow-up visits to staff paediatricians. In addition, a medical compliance questionnaire was completed anonymously by parents 1 month after post-test assessments. 91.9% of parents in the medication conditions indicated that their child took the stimulant medication almost every day throughout the study, whereas nearly all remaining families reported average usage of 3 to 4 days a week |

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|---|---|
| Outcomes | **ADHD symptoms**<br>1. Conners' Parent Rating Scale<br>2. Conners' Teacher Rating Scale<br>**General behaviour**<br>1. Conners' Teacher Rating Scale, Conduct problems |
| Notes | Sample calculation: no information<br>Ethics approval: no information<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Key conclusion of study authors**<br>1. In contrast to placebo, although methylphenidate resulted in significantly greater amelioration of many of the core features of ADHD, we found no evidence of a decrease in perceived competence, or of an increase in external or unknown explanations of control or dysphoria at post-test (i.e. 14 weeks later)<br>Email correspondence with study authors: August 2013 and January 2014. We emailed study authors to request a copy of the protocol and additional information on, for example, the randomisation procedure and funding |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomly assigned |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | All medication was dispensed in a double-blinded fashion |
| Blinding of outcome assessment (detection bias) | Low risk | All medication was dispensed in a double-blinded fashion |
| Incomplete outcome data (attrition bias) | High risk | No description of imputation method |
| Selective reporting (reporting bias) | Unclear risk | No information |
| Vested interest bias | Unclear risk | No information |

### *Jacobi-Polishook 2009*

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|---|---|
| Methods | Single-day, randomised, controlled, parallel, double-blind study with 2 arms investigating postural stability in 24 children with ADHD<br>1. Methylphenidate<br>2. Placebo |

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|---|---|
| Participants | Number of participants screened: 80<br>Number of participants included: 24<br>Number randomly assigned: methylphenidate 12 (11 boys, 1 girl), placebo 12 (11 boys, 1 girl)<br>Number of participants followed up in each arm: methylphenidate 12, placebo 12<br>Number of withdrawals in each arm: methylphenidate 0, placebo 0<br>Diagnosis of ADHD: DSM-IV (subtype not stated)<br>Age: methylphenidate mean 10.06 years (range 7 to 16), placebo mean 10.88 years (range 7 to 16)<br>Methylphenidate naive: 0%<br>Ethnicity: Israeli<br>Country: Israel<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: no<br>IQ: > 70<br>Sociodemographics: not stated<br>**Differences between groups**<br>1. No significant difference in baseline demographics were noted between the 2 groups<br>**Inclusion criteria**<br>1. DSM-IV diagnosis<br>2. 7 to 16 years of age<br>3. Methylphenidate treatment on a daily basis for the past 3 months<br>4. Only methylphenidate responders (improvement in ADHD symptoms after methylphenidate treatment according to parent and teacher reports on the ADHD Rating Scale, Fourth Edition, and according to paediatric neurologist follow-up)<br>5. IQ > 70<br>6. ADHD symptoms had to be severe for ≥ 6 items on the DSM-IV ADHD Rating Scale (ADHD RS-IV), Parent Version<br>**Exclusion criteria**<br>1. Neurological, orthopaedic or psychiatric diagnoses according to DSM-IV criteria that can affect motor control and postural stability: cerebral palsy, neuropathic disease, limb fracture or head trauma during the previous year<br>2. Use of any medication other than methylphenidate during the study period |
| Interventions | Participants were randomly assigned to 5 mg of short-acting methylphenidate or 5 mg placebo. They had been drug-free for 24 hours before the start of the trial<br>Administration schedule: 5 mg × 1 (single dose)<br>Duration of intervention: 1 day<br>Titration period: none<br>Treatment compliance: 100% |
| Outcomes | **Serious adverse events**<br>1. No serious adverse events of drug treatment were experienced<br>**Non-serious adverse events**<br>1. No non-serious adverse events of drug treatment were experienced |

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|---|---|
| **Notes** | Sample calculation: yes<br>Ethics approval: no information<br>**Key conclusions of study authors**<br>1. Methylphenidate improves postural stability in ADHD, especially when an additional task is performed, probably through enhanced attention abilities, thus contributing to improved balance control during performance of tasks that require attention<br>2. Methylphenidate remains to be studied as a potential drug treatment to improve balance control and physical functioning in other clinical populations<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; see 'Inclusion criteria'<br>Any withdrawals due to adverse events: no |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomisation using a table of random numbers |
| Allocation concealment (selection bias) | Low risk | Placebo pill was identical in appearance to the methylphenidate pill |
| Blinding of participants and personnel (performance bias) | Low risk | Participants and tester administering the examination were blinded to group assignments |
| Blinding of outcome assessment (detection bias) | Low risk | Participants and tester administering the examination were blinded to group assignments |
| Incomplete outcome data (attrition bias) | Low risk | No drop-outs in either group |
| Selective reporting (reporting bias) | Low risk | Outcomes reported according to protocol |
| Vested interest bias | Unclear risk | No information |

### *Jensen 1999 (MTA)*

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| **Methods** | Multimodal Treatment Study of Children With ADHD (MTA) (Jensen 1999 (MTA)): 14-month multi-centre, randomised, parallel clinical trial with 4 arms<br>1. Medication management<br>2. Behavioural treatment<br>3. Combined treatment (medication management + behavioural treatment)<br>4. Community care (control group)<br>Phases: For the 2 groups receiving medication, an initial 28-day titration period was provided. This titration phase was carried out as a randomised, double-blind, placebo-controlled, cross-over trial with daily switching of methylphenidate doses (placebo, low, middle and high). Once delivery of randomly assigned treatments by MTA staff stopped at 14 months, the MTA became an observational study in which participants and families were free to choose their own treatment, but in the context of availability and barriers to care existing in their communities. The following follow-up assessments took place after completion of the RCT at 10 months' follow-up (24 months after randomisation), 3-year follow-up, 8-year follow-up and 10-year follow-up<br>In our review, we will compare combined behavioural treatment (RCT) according to our protocol and will look at the medication treatment group as a cohort (observational) |
| **Participants** | **Titration period (Greenhill 2001) (** Jensen 1999 (MTA) **)**<br>28-day RCT (combined treatment + medication management group)<br>Number of participants included: 289 (medication management 144, combined treatment 145) |

Number of participants completed: 256

Number of participants not finishing titration: 33. Of the completers, 198 were assigned to an individually best dose of methylphenidate for the 14-month trial, the rest to other medication or no medication

**Main study (Jensen 1999) (** Jensen 1999 (MTA) **)**

Number of participants screened: 4541

Number of participants included: 579

Number of participants randomly assigned to methylphenidate + behavioural treatment (combined treatment): 145, MPH 144, behavioural treatment (BEH) 144

Number of participants followed up: combined treatment 142; medication 136; behavioural treatment 141

Number of withdrawals/drop-outs: combined treatment 3; medication 8; behavioural treatment 3

**Demographic data for combined treatment, behavioural treatment and medication management**

Diagnosis of ADHD: DSM-IV (combined (100%))

Age: mean 8.4 years (range 7 to 9.9)

IQ: mean 100.4

Sex: 346 boys, 87 girls

Methylphenidate naive: 177

Ethnicity: White (60.3%), African American (20.6%), Hispanic (8.8%), other (10.4%)

Country: USA and Canada

Setting: out-patient clinic

Comorbidity: anxiety disorder (35.1%), conduct disorder (14.1%), oppositional defiant disorder (38.8%), affective disorder (3.5%), tic disorder (10.2%), mania/hypomania (3%)

Comedication: not stated

Sociodemographics: 130 families on welfare. Population ranges widely in socioeconomic status. No significant differences in baseline demographics were noted between the 3 groups

**10-Month follow-up (MTA Group 2004) (** Jensen 1999 (MTA) **)**

Number of participants followed up in each arm: MGT 128, COMB 138, BEH 139; age (mean 8.4 years); sex (322 boys, 83 girls). No differences between demographic characteristics of the originally randomly assigned 579 MTA participants and participants assessed during 10-month follow-up. The only statistically significant difference among treatment groups was a trivial difference in age (MHT was 0.3 years older than BEH)

**3-Year follow-up (Jensen 2007) (** Jensen 1999 (MTA) **)**

Number of participants followed up: medication 115, combined treatment 127

Age: mean 11.7 years (range 10 to 13)

Sex: 291 boys, 78 girls

No significant differences in baseline characteristics were noted between participants in the 36-month assessment and those unable to be followed

**8-Year follow-up (Molina 2008) (** Jensen 1999 (MTA) **)**

Number of participants followed up: medication management 101, combined treatment 119. 32.5% of the MTA sample was medicated more than 50% of days the previous year

Age: mean 16.8 years (range 13 to 16). At 8-year assessment, 55 MTA participants had turned 18 years of age. Only 30% of the sample still fulfilled an ADHD diagnosis. Participants lost to 8-year follow-up, compared with those retained, more often were male; had younger mothers, less educated parents and lower parent income; and were more likely to have been on welfare at baseline

**10-Year follow-up, blood pressure (Vitiello 2012) (** Jensen 1999 (MTA) **)**

Number of participants followed up: medication management 77, combined treatment 93. A comparison of participants retained through the year 10 (n = 346) vs those who were not (n = 233) showed a smaller proportion of males in the retained group. Furthermore, participants were divided into groups on the basis of the following criteria: "never medicated", currently medicated, previously medicated. For the currently medicated group, numbers of participants were, respectively, 184, 184, 108, 50 and 12 for 24 months, 36 months, 72 months, 96 months and 120 months of follow-up, respectively. Medication use during the previous 30 days was the criterion for positive medication status

**Growth studies, 24-month assessment (Jensen 2004) (** Jensen 1999 (MTA) **)**

For growth outcomes, data from both the originally randomly assigned treatment groups and naturalistic subgroups were collected. Naturalistic subgroups consisted of those who had been medicated at all assessment points up to 24 months (medication use during previous 30 days was the criterion for positive medication status) and those who had not been medicated at assessment points

Participants with consistent use of medication (med/med): 255

Participants with no use of medication (NoMed/NoMed) 139; combined treatment 135, medication management 120

**Growth studies, 36-month assessment (Swanson 2007) (** Jensen 1999 (MTA) **)**

Naturalistic subgroups were established on the basis of patterns of treatment with stimulant medication. If medication was used within a 30-day period before assessment, medication status was positive (Med); otherwise it was negative (NoMed). If an individual's medication status changed at any assessment point, he or she was placed in the inconsistently medicated group

Participants with Med (n = 70). At baseline and at 14-, 24- and 36-month assessment points, respectively, percentages of medicated children taking methylphenidate were as follows: 85.4%, 79.7%, 76.8%, 73.5%. Naturalistic subgroups did not differ in initial size at birth (birth weight), age, parent or teacher ratings of ADHD symptoms, sex, expected adult size (mid-parent size), welfare status or maternal smoking

**Inclusion criteria**

1. Boys and girls
2. 7 to 9. 9 years of age
3. Grades 1 through 4
4. In residence with the same primary caretaker(s) for the past 6 months or longer
5. Meeting DSM-IV criteria for ADHD, combined type.

**Exclusion criteria**

1. Child currently in hospital
2. Child currently in another study
3. < 80 on all Weschler Intelligence Scales for Children, Third Edition, and on Severe Impairment Battery (SIB) (bipolar disorder, psychosis or personality disorder)
4. Chronic serious tics or Tourette's syndrome
5. Obsessive-compulsive disorder serious enough to require separate treatment
6. Neuroleptic medication in previous 6 months
7. Major neurological or medical illness
8. History of intolerance to MTA medications
9. Ongoing or previously unreported abuse
10. Missed one-fourth of school days in previous 2 months
11. Same classroom as child already in MTA study
12. Parental stimulant abuse in previous 2 years
13. Non-English-speaking primary caretaker
14. Another child in same household in MTA study
15. No telephone
16. Suicidal or homicidal

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| Interventions | **Titration period (Greenhill 2001) (** Jensen 1999 (MTA) **)**<br>Mean methylphenidate dose during titration period: combined treatment 32.1 mg/d, medication management 28.9 mg/d. Medication management started with a 4-day single-blind, safety lead-in period, during which participants were exposed to 3 progressively higher daily methylphenidate doses given 3 times daily. This was followed by a 28-day, double-blind, daily, switch titration of methylphenidate hydrochloride, with 5 randomly ordered repeats each of placebo, 5 mg, 10 mg and 15 mg or 20 mg. Cross-site teams of experienced clinicians blindly reviewed graphs portraying parent and teacher ratings of responses to each of the 4 doses and by consensus selected each child's best dose<br>Compliance: not stated. 29 of 32 placebo responders had to go back to taking methylphenidate during the maintenance period<br><br>**Main study (Jensen 1999) (** Jensen 1999 (MTA) **)**<br>Participants were randomly assigned to medication management, behavioural treatment or combined treatment<br>Mean methylphenidate dosage during main study: combined treatment 31.2 mg/d, medication management: 37.8 mg/d<br>Administration schedule: 3 times a day - breakfast, lunch and in the afternoon<br>Duration of intervention: 14 months<br>Treatment compliance: monthly pill counts, intermittent saliva measurements to monitor intake of methylphenidate and encouragement for families to make up missed visits. "The study achieved a high degree of adherence to protocol." NB! For participants not attaining an adequate response to methylphenidate during titration, alternate medications were titrated openly in the following order until a satisfactory choice was found: dextroamphetamine, pemoline, imipramine and others, if necessary approved by a cross-site panel. Thus, 256 participants successfully completed titration; of these, 198 of 289 participants were assigned to an individually titrated best dose of methylphenidate, and 26 were titrated to dextroamphetamine. 32 were given no medication because of a robust placebo response<br><br>**10-Month follow-up (MTA Group 2004) (** Jensen 1999 (MTA) **)**<br>Duration of intervention: 24 months (10-month follow-up from 14-month RCT)<br>Treatment compliance: not stated. From end of treatment to first follow-up, percentage of participants taking medication decreased for combined treatment (87% vs 70%) and methylphenidate (93% vs 72%) but increased for behavioural intervention (23% to 38%)<br><br>**3-Year follow-up (Jensen 2007) (** Jensen 1999 (MTA) **)**<br>Duration of intervention: 3 years (36-month follow-up from 14-month RCT)<br>Treatment compliance: not stated. At 36 months, percentage of participants taking medication was 70% for the combined group, 72% for the methylphenidate group and 45% for the behavioural intervention group<br><br>**8-Year follow-up (Molina 2009) (** Jensen 1999 (MTA) **)**<br>Duration of intervention: 8 years<br>Mean methylphenidate dosage: 44.93 mg<br><br>**10-Year follow-up (Vitello 2012) (** Jensen 1999 (MTA) **)**<br>Duration of intervention: 10 years<br>Treatment compliance: not stated<br>Mean methylphenidate dosage: 54.3 mg |
| Outcomes | **Titration period (Greenhill 2001) (** Jensen 1999 (MTA) **)**<br>• Conners' Lonely and Milich Questionnaire (with Inattention/Overactive (I/O))<br>• Aggressive/Defiant (A/D) and Mixed (I/O + A/D) subscales: assessed daily by |

parents and teachers
- Swanson, Kotkin, Agler, M-Flynn and Pelham (with Attention and Deportment subscales): rated daily by parents and teachers

**Main study (Jensen 1999)**

- SNAP Inattention and Hyperactivity-Impulsivity subscale, both parent and teacher: assessed at baseline and at 3, 9 and 14 months
- SNAP Oppositional Defiant Disorder subscale, both parent- and teacher-rated: assessed at baseline and at 3, 9 and 14 months.
- Abikoff Classroom Observational System (ADHD and oppositional/aggressive symptoms): blind ratings by blind observers

**Serious adverse events**

**Main study (Jensen 1999)**

1. 6 of 11 reported severe side effects could have been due to non-medication factors
2. Three deaths were recorded among ADHD participants during 10 years of observation: a suicide at age 14 (participant was taking methylphenidate), a fatal car accident at age 17 (participant was the driver and was taking methylphenidate) and a sudden unexplained death at age 17 (participant was found dead in bed; no specific cause of death could be determined; he had been treated previously with methylphenidate and had been off medication for longer than 1 year when he died)

**Non-serious adverse events**

**Main study (Jensen 1999)**

Participants were provided up to 8 additional sessions when needed to address clinical emergencies or instances of possible study attrition

1. Pittsburgh Side Effects Rating Scale: monitored monthly, reviewed by the pharmacotherapist
2. Internalising symptoms (anxiety and depression): measured with an internalising subscale from parent- and teacher-completed Social Skills Responsive Scale (SSRS), measured at baseline and at 3, 9 and 14 months
3. Children's self ratings on the Multidimensional Anxiety Scale for Children: assessed at baseline and at 3, 9 and 14 months

**Titration period (Greenhill 2001) (** Jensen 1999 (MTA) **)**

1. Pittsburgh Side Effects Rating Scale (10 adverse events commonly associated with methylphenidate were rated)

**3-Year follow-up (Molina 2007) (** Jensen 1999 (MTA) **)**

1. Substance abuse: assessed at 24 and 36 months by a child-reported substance use questionnaire (Molina and Pelham, 2003) adapted for the MTA. The measure included items for lifetime and current (past 6 months) use of licit substances (alcohol, cigarettes, chewing tobacco) and illicit drugs (marijuana and other street drugs). Also included were items for inappropriate or non-prescribed use of medications, including stimulants
2. Delinquency: assessed by the Self-Reported Antisocial Behavior Questionnaire through 24-month assessment and the Self-Reported Delinquency Questionnaire at 36-month assessment. Delinquency was coded along an ordinal scale on the basis of the most serious act committed during the past 6 months: 0 = no delinquency; 1 = minor delinquency only at home (e.g. theft of less than $5 or vandalism); 2 = minor delinquency outside the home (e.g. vandalism, cheating someone, shoplifting less than $5); 3 = moderately serious delinquency (e.g. vandalism, theft of $5 or more, weapon carrying); 4 = serious delinquency (e.g. breaking and entering, drug selling, attacking someone with the intent to seriously hurt or kill, rape); and 5 = engagement in 2 or more different Level 4 offences. Because only a small number of MTA children were coded 5 (n = 14 at baseline, n = 4 and 5 between 14 and 36 months), we grouped codes 4 and 5 for data analyses, making a 5-level ordinal scale of 0 to 4

**8-Year follow-up (Molina 2009) (** Jensen 1999 (MTA) **)**

1. Delinquent behaviour coded on a 5-point ordinal scale using parent and youth report across several measures
2. Number of contacts with police and arrests using the Services for Children and Adolescents-Parent Interview, parent reported
3. Depression rated by the Children's Depression Inventory, self rated
4. Anxiety rated with by Multidimensional Anxiety Scale for Children, self rated

5. Psychiatric hospitalisation by 8 years, parent reported

**8-Year follow-up, substance abuse (Molina 2009) ( Jensen 1999 (MTA) )**

1. Substance use: assessed by a child/adolescent-reported questionnaire adapted for the MTA. Substance use outcomes were measured at all interviews beginning with 24-month assessment

For analysis of stimulant treatment duration in relation to substance use at 8-year follow-up, the primary outcome was the number of substances used in the past 6 months, to ensure that most stimulant treatment received would have preceded substance use. Component variables included the following: "drunk" once or more or drank alcohol 3 to 4 or more times; 1 or more cigarettes per day in the past month (time frame exception specific to tobacco); marijuana 2 or more times; and any other illicit drug use or prescription medication misuse. Secondary analyses explored each class of substances separately. For analysis of stimulant treatment exposure over time in relation to substance use at 8-year follow-up, the primary outcome variable was substance use disorder in the past year for any substance (excluding tobacco). Secondary analyses explored alcohol and marijuana/other drug use disorders separately

**10-Year follow-up (Vitello 2012) ( Jensen 1999 (MTA) )**

1. Blood pressure and heart rate monitoring, measured after participants had been sitting for 5 minutes, adjusted for age and sex
2. Height and weight
3. Hospitalisation measured at each assessment point
4. No symptomatic cardiovascular events leading to medical attention were reported during the period of observation, and no stimulant treatment discontinuation consequent to cardiovascular adverse effects occurred during the 10-year period

**Growth (Jensen 2004, Swanson 2007) ( Jensen 1999 (MTA) )**

1. Height in centimeters and weight in kilograms, assessed at baseline, 14 months, 24 months and 36 months

**Notes**

Sample calculation: yes; power analysis, with 576 participants required

Ethics approval: yes; approved by both local institutional review boards and National Institutes of Health Office for Protection From Research Risk

Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no

Any drop-outs due to adverse events: Four participants were removed during the lead-in (titration period) because of prohibitive side effects: 1 child with buccal movements; another with skin picking; a third with depression, crying, sleep delay and appetite loss; and a fourth who was anorexic, listless and emotionally constricted

**Comments from study authors**

1. **Main study (Jensen 1999)**
   a. Recruitment, screening and selection procedures aimed to collect a carefully diagnosed sample of impaired children with ADHD and a wide range of comorbid conditions and demographic characteristics representative of patients seen in clinical practice
   b. The design did not include a no-treatment or placebo group
   c. More than three-fourths of participants given behavioural treatment were successfully maintained without medication throughout the study. Consequently, it should not be concluded that behavioural treatment interventions did not work
   d. Combined treatment and medication management were clinically and statistically superior to behavioural treatment and community care in reducing children's ADHD symptoms. (...) For other areas of function (oppositional/aggressive behaviours, internalising symptoms, social skills, parent-child relations and academic achievement), few differences among our treatments were noted, and when found, were generally of smaller magnitude
   e. Significantly lower total daily dose of methylphenidate in the combined treatment arm is noteworthy but was not unforeseen. The importance of this finding is unclear, and a rigorous test of the question would likely require a different design
2. **Titration period (Greenhill 2001) ( Jensen 1999 (MTA) )**
   a. Short 28-day duration limited generalisability to long-term treatment
   b. Rates of response to methylphenidate ran between 70% and 80% within the expected range

c. MTA titration study showed a steeper dose-response curve for younger and lighter children with ADHD
d. When ratings were collected under placebo-controlled, double-blind conditions, parents reported more adverse events than did teachers. For this reason, clinicians would be wise to collect methylphenidate side effect ratings from parents in the afternoons and evenings

3. **10-Month follow-up (MTA Group 2004) (** Jensen 1999 (MTA) **)**
   a. At follow-up, dose levels of medication management participants (in methylphenidate equivalents) were significantly higher than those of participants in the combined treatment group. Interesting results suggest the possibility that early combined treatment interventions might allow reduced overall medication requirements during later periods, consistent with findings reported by others
4. **3-Year follow-up (Jensen 2007) (** Jensen 1999 (MTA) **)**
   a. By 36 months, none of the randomly assigned treatment groups differed significantly in any of the 5 clinical and functional outcomes. (..) However despite no significant group differences at 36-month assessment, substantial improvement was manifested by all groups. As no untreated control groups were included, and because all treatment groups were improved in terms of relevant symptoms at 36 months compared with baseline, it is possible that all treatments worked but at different rates in different time periods
   b. It is interesting that both medication and educational services provided for 24 to 36 months were markers for poorer outcome at 36 months, suggesting that those who are doing poorly are given additional treatment, yet still do not do as well as those for whom treatment is not considered essential
5. **Vitiello 2001 (** Jensen 1999 (MTA) **)**
   a. Comorbid anxiety, oppositional defiant disorder or conduct disorder was not associated with statistically significant differences in methylphenidate dose at the end of titration or maintenance, the number of medication changes or the time to first change
   b. A short-term response to placebo occurred in 32 children (of 256 who completed double-blind titration) but was maintained in only 3 patients over the long term
6. **Conners 2001 (** Jensen 1999 (MTA) **)**
   a. It is clear that the treatment effect in this study depends on the choice of endpoint measure. Results highlight the fact that no "one true outcome" can be found for a randomised clinical trial, because different measures may be sensitive to different forms of treatment
7. **8-Year follow-up (Molina 2008) (** Jensen 1999 (MTA) **)**
   a. Across time (to 8-year follow-up), 17.2% of children were medicated at every assessment, beginning with the 14-month report
8. **10-Year follow-up (Vitiello 2012) (** Jensen 1999 (MTA) **)**
   a. This clinical trial was not specifically designed to evaluate cardiovascular function
   b. Blood pressure and heart measurements were not conducted under double-blind conditions, and measurement methods varied across clinical sites
   c. Abnormal blood pressure values were not systematically confirmed over 3 separate assessments, as required for a diagnosis of pre-hypertension or hypertension
   d. Time of day when measurements were taken was variable
9. **Implications and applications for primary care providers (Jensen 2001) (** Jensen 1999 (MTA) **)**
   a. Behavioural treatments may help families actively cope with their child's disorder while making necessary life accommodations to optimise family functioning, even when such treatments are not as effective as medication in reducing symptoms of children with ADHD
   b. Findings suggest that high-quality treatments may have considerable impact on restoring children with ADHD to normal or near-normal functioning at home and in the classroom. Because essentially none of the children with ADHD met the normal criteria met by 88% of comparison children drawn from the same classrooms at study outset, the notion that ADHD is just normal behaviour labelled by uninformed parents or overwhelmed teachers appears not only implausible, but preposterous
10. **W.E. Pelham 1999 (** Jensen 1999 (MTA) **)**
    a. Two major treatment modalities - behavioural and pharmacological - were assessed at different time points relative to the intensive phase of treatment. Specifically, the effects of pharmacological treatments were assessed at post treatment, while participants were actively medicated; in contrast, the effects of behavioural treatment were assessed after therapist involvement diminished. The

intensive period of behavioural treatment ended in late December or early January, and endpoint measures typically were taken 4 to 6 months later - usually several months after the last planned, face-to-face therapeutic contact. This design aspect has numerous implications for interpretation of study findings. For example, we cannot state that the medication (methylphenidate for the vast majority) had long-term effects. Rather, results simply demonstrate that effects of methylphenidate given steadily for 14 months are the same at the end of that time as at the beginning (indeed the correlations between drug effects at these 2 points of the study are very high). When differences in outcomes between these groups (e.g. behavioural therapy, medication management) are analysed, data suggest it is likely that combined treatment for children whose parents and teachers continued the behavioural interventions they had been taught will have outcomes superior to those of medication management, and outcomes with combined treatment for those whose parents and teachers did not continue behavioural treatment will be equivalent to those with medication management alone (which would not be surprising, as functionally this is what they would be receiving)

11. **Growth, 24-month outcomes (Jensen 2004) (** Jensen 1999 (MTA) **)**
    a. Growth suppression effects could be related to a medication effect, with the continuously treated subgroup showing slower growth than the untreated subgroup. Alternatively, the "Continuously treated subgroup", defined by unknown self selection factors, could have had a slower growth rate before the start of the study, which continued during treatment and follow-up phases of the MTA. Our data cannot permit a determination of the validity of these alternative interpretations. At this first follow-up, our observations were of children in the MTA when they were between the ages of 9 and 11 years, which is before the expected phase of accelerated growth in adolescence and before the age when growth is expected to slow and final height is approximated. Rate of growth and length of the growth phase together determine ultimate (adult) height, and it is possible that consistent treatment with medication may reduce the rate but lengthen the duration of growth, so final height would be delayed but not reduced. It is possible that the never-medicated group was pared down to good responders and the medicated groups were enriched by poor behavioural responders. In the analysis of 14- to 24-month change scores, "Medication status" was significant for both height ($X^2$ = 16.16, P value < 0.001) and weight ($X^2$ = 13.32, P value < 0.004)
12. **Growth, 36-month assessment (Swanson 2007) (** Jensen 1999 (MTA) **)**
    a. We did not document a decrease in relative size among the group of participants with a history of treatment before entry into the MTA protocol during subsequent treatment with stimulant medication over 3 years. However, this group (the consistently medicated naturalistic subgroup) was smaller than the stimulant naive group (the newly medicated naturalistic subgroup at entry), suggesting that early treatment of children (before 7 to 9 years of age) with stimulant medication may have produced a reduction in growth rate before entry into the MTA protocol

**Key conclusions of study authors**

1. **Main study (Jensen 1999)**
    a. For ADHD symptoms, our carefully crafted medication management was superior to behavioural treatment and to routine community care that included medication. Our combined treatment did not yield significantly greater benefits than medication management for core ADHD symptoms but may have provided modest advantages for non-ADHD symptoms and positive functioning outcomes
2. **Vitiello 2001 (** Jensen 1999 (MTA) **)**
    a. For most children, initial titration found a dose of methylphenidate in the general range of the effective maintenance dose but did not prevent the need for subsequent maintenance adjustments. For optimal pharmacological treatment of individuals with ADHD, both careful initial titration and ongoing medication management are needed
3. **Titration period (Greenhill 2001) (** Jensen 1999 (MTA) **)**
    a. The MTA titration protocol validated the efficacy of weekend methylphenidate dosing and established a total daily dose limit of 35 mg of methylphenidate for children weighing < 25 kg. It replicated previously reported methylphenidate response rates (77%), distribution of best doses (10 mg/d to 50 mg/d) across participants, effect sizes on impairment and deportment and dose-related adverse events. With t.i.d. dosing, the MTA titration trial showed that significant stimulant medication effects on ADHD symptom reduction and drug-related adverse events could be detected by parents and teachers by using daily ratings

under controlled conditions

4. **10-Month follow-up (MTA Group 2004) (** Jensen 1999 (MTA) **)**
   a. The benefits of intensive medical intervention for ADHD extend 10 months beyond the intensive treatment phase only in symptom domains and diminish over time.
5. **3-Year follow-up (Jensen 2007) (** Jensen 1999 (MTA) **)**
   a. By 36 months, the earlier advantage of having had 14 months of the medication algorithm was no longer apparent, possibly because of age-related decline in ADHD symptoms, changes in medication management intensity, starting or stopping of medications altogether or other factors not yet evaluated. At 24 and 36 months, investigators assessed delinquency and substance abuse
6. **Molina 2007 (** Jensen 1999 (MTA) **)**
   a. Cause-and-effect relationships between medication treatment and delinquency are unclear; absence of associations between medication treatment and substance use must be re-evaluated at older ages
   b. Findings underscore the need for continuous monitoring of these outcomes as children with attention deficit hyperactivity disorder enter adolescence. No statistically significant effects of randomly assigned treatment on individual rate of change in delinquency were observed between baseline and 36 months at the P value < .05 level. Results suggest that increasing delinquency between 24 and 36 months was associated with an increase in substance use during the same time period. We found no evidence of protective or adverse effects of medication treatment for ADHD in either study
7. **8-Year follow-up (Molina 2009) (** Jensen 1999 (MTA) **)**
   a. Type or intensity of 14 months of treatment for ADHD in childhood (at age 7 to 9.9 years) does not predict functioning 6 to 8 years later. Rather, an early ADHD symptom trajectory regardless of treatment type is prognostic. This finding implies that children with behavioural and sociodemographic advantages, with the best response to any treatment, will have the best long-term prognosis. As a group, however, despite initial symptom improvement during treatment that is largely maintained after treatment, children with combined-type ADHD exhibit significant impairment in adolescence. Innovative treatment approaches targeting specific areas of adolescent impairment are needed
8. **10-Year follow-up, blood pressure (Vitiello 2012) (** Jensen 1999 (MTA) **)**
   a. Stimulant treatment did not increase the risk for pre-hypertension or hypertension over the 10-year period of observation. However, stimulants had a persistent adrenergic effect on heart rate during treatment
9. **Growth studies, 24-month follow-up (Jensen 2004) (** Jensen 1999 (MTA) **)**
   a. In the MTA follow-up, exploratory naturalistic analyses suggest that consistent use of stimulant medication was associated with maintenance of effectiveness but continued mild growth suppression
10. **Growth studies, 3-year follow up (Swanson 2007) (** Jensen 1999 (MTA) **)**
    a. Combined-type attention-deficit hyperactivity disorders were, as a group, greater than expected from norms before treatment but show stimulant-related decreases in growth rate after initiation of treatment, which appeared to reach asymptotes within 3 years without evidence of growth rebound
11. **W.E. Pelham 1999 (** Jensen 1999 (MTA) **)**
    a. Active medication for ADHD is better than withdrawn behavioural treatment (on some but not most measures)
    b. Combined treatment adds modestly to active medication but is superior to behaviour management alone
    c. Study treatments that include active medication are better than community treatments that include medication, and behavioural treatment is comparable with medication as delivered in the community
    d. Concurrent BT results ≥ 20% lower and increasing medication dosages relative to treatment with medication alone
12. **Comorbidity (Jensen 2001) (** Jensen 1999 (MTA) **)**
    a. Our findings suggest that children with ADHD with and without oppositional defiant disorder/conduct disorder and anxiety differed in many baseline characteristics, outcomes and response to treatment. Children with anxiety tended to be more treatment-responsive than those with ADHD + oppositional defiant disorder/conduct disorder, and even ADHD-only participants
13. **Anxiety (March 2000) (** Jensen 1999 (MTA) **)**
    a. Contravening earlier studies, no adverse effects of anxiety on medication response for core ADHD or other outcomes in anxious or non-anxious ADHD children was demonstrated. When ADHD is treated, it is important for

practitioners to search for comorbid anxiety and negative affectivity and to adjust treatment strategies accordingly

14. **Swanson 2007 (** Jensen 1999 (MTA) **)**
    a. Long-term benefits of consistent treatment were not documented; selection bias was not shown to account for loss of relative superiority of medication over time; no evidence of "catch-up" growth was found; early treatment with medication did not protect against later adverse outcomes. We expect that these challenges to views of practitioners will contribute to future controversy about long-term outcomes of the MTA
15. **Molina 2012, substance use (** Jensen 1999 (MTA) **)**
    a. Our findings provide no evidence that ADHD medication protects from, or increases risk for, adolescent substance use, or SUD. This finding held for recent medication and for days of cumulative treatment with stimulants. Unmeasured confounders may have been operating because of the naturalistic follow-up study design, and we did not statistically control for psychopathology and functioning at follow-up assessment. Observed lack of association between stimulant exposure over time and adolescent substance use/SUD does not eliminate the possibility that brain-based changes in neural mechanisms underlying addiction vulnerability are occurring as a function of prolonged stimulant treatment. Substance use/SUD outcomes for the MTA should be considered in the context of several unique study features and limitations. All children in the MTA were diagnosed with the combined type of DSM-IV ADHD, and generalisation of study results generally should not extend beyond this subtype. Our follow-up assessments, which relied on self report, often with 2-year windows, might have missed episodes of substance use, and rates may be underestimated
16. **Pelham 2000 (** Jensen 1999 (MTA) **)**
    a. The Diagnostic Interview Schedule for Children interview shows that 75% of children in the behavioural treatment group were maintained without medication for 14 months, and 64% did not meet diagnostic criteria for ADHD at 14 months (MTA Cooperative Group, 1999, 1999a). Such findings highlight the fact that intensive behavioural treatments are a viable alternative to medication for treatment of individuals with ADHD

**Comments from review authors**

1. Authors from the MTA study have written more than 70 articles describing different outcomes and challenges of the study. We have included only those found through our comprehensive literature search and others that we found relevant to include upon looking through article reference lists
2. We have discussed whether to include the MTA study, as not all participants randomly assigned to medication (combined treatment and medication management group) received methylphenidate. Those who did not have an adequate response to methylphenidate were given other medication (e.g. dextroamphetamine, pemoline, imipramine) or no medication. Furthermore, some participants in the BEH group were also medicated during the 14-month randomisation phase. From all other studies in this review, we have included only receivers of pure methylphenidate. Furthermore, lots of participants did not have an ADHD diagnosis at follow-up assessment. At 8-year follow-up, only 30% of remaining participants still had a diagnosis of ADHD. However, we have chosen to use the data from MTA, as it is such a large and well-known study. All MTA analyses will be included in the review as sensitivity analyses
3. Regarding Molina 2012 (substance use): We have included/asked for additional data from this study, even though the medicated group received medication for a mean of only 2071.10 (SD 728.87) days of the 8 years the follow-up took place
4. The following articles from the MTA study have been assessed by only 1 review author: Pelham 2000, Carey 2000, Swanson and Hinshaw 2007, Galanter 2003, Hinshaw 1999, Molina 2013

Email correspondence with study authors: January 2014 to June 2014. We sent several emails to the MTA group to request additional information. However, we were not able to obtain additional data. We did receive an email from Dr. Hinshaw confirming that the data on ADHD symptoms, parent-rated, were wrong - instead of a mean of 1.85, the correct mean was 0.85 for combined treatment after 14 months. We also received an email from Dr. Swanson in June 2014 stating that he would help with data collection. We wanted to conduct a reanalysis of data excluding those few participants not receiving methylphenidate. Dr. Swanson proved several helpful comments on this and enclosed published articles, but we did not receive additional

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| | data, in part because of the time frame of this review |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomisation was done centrally by the National Institute of Mental Health (NIMH) Data Center, stratified by site in blocks of 16 (4 to each group). Stratified by 6 sites. Sealed, ordered envelopes were sent to sites for successive entries |
| Allocation concealment (selection bias) | Low risk | Sealed, ordered envelopes were sent to sites for successive entries. Treatment assignment was concealed until the family confirmed agreement to accept randomisation |
| Blinding of participants and personnel (performance bias) | High risk | Treatment assignment was concealed until the family confirmed agreement to accept randomisation. After agreement on best dose, the blind was broken, and the agreed on dose (if not placebo) became the participant's initial maintenance dose |
| Blinding of outcome assessment (detection bias) | High risk | After agreement on best dose, the blind was broken, and the agreed on dose (if not placebo) became the participant's initial maintenance dose. However, for some outcome measures, 3 strategies were devised to enlist blinded raters and objective observations |
| Incomplete outcome data (attrition bias) | Low risk | ITT analyses. Despite high compliance, we checked whether compliance with assessments (i.e. missing data) could have changed our findings. Random-effects regression analyses were completed 2 ways: once with inclusion of all participants, and then including only participants who provided data over multiple time points during the study. No differences emerged from these 2 sets of analyses |
| Selective reporting (reporting bias) | Low risk | This study was supported by several grants from the National Institute of Mental Health (NIMH), Bethesda, Maryland |
| Vested interest bias | Low risk | This study was supported by several grants from the National Institute of Mental Health, Bethesda, Maryland<br>Conflicts of interest: Several study authors have affiliations with medical companies |

*Johnston 1988*

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| Methods | Two-week cross-over trial with 3 interventions<br>1. Methylphenidate<br>2. Placebo<br>3. Sustained-release methylphenidate (we do not report on this group here)<br>Phases: to define rebound effects in 21 boys 4 to 10 years of age, with a DSM-III diagnosis of ADD and treated with methylphenidate some days, and placebo other days |

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| Participants | Number of participants screened: not stated<br>Number of participants included: 21. Participants were assigned to different orders of methylphenidate and placebo<br>Number of participants followed up: 21 (21 boys, 0 girls)<br>Number of withdrawals: 0<br>Diagnosis of ADD: DSM-III-R (subtype not stated)<br>Age: mean 7 years 7 months (range 4 to 10 years)<br>IQ: mean 101 (range 79 to 120)<br>Methylphenidate naive: not stated<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic (summer treatment programme)<br>Comorbidity: conduct disorder (n = 2), oppositional defiant disorder (n = 17), learning disability (n = 9)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. DSM-III-R diagnosis of ADD<br>**Exclusion criteria**<br>1. Not stated |
| Interventions | Random sequence allocation to<br>1. 0.3 mg/kg methylphenidate twice daily (at breakfast and just before lunch; n = 21)<br>2. 0.6 mg/kg methylphenidate twice daily (at breakfast and just before lunch; n = 16 of the same 21 participants)<br>3. 20 mg sustained-release methylphenidate (n = 8). Not reported here<br>4. Placebo<br>Within-participant random sequence, condition varied daily<br>Mean methylphenidate dosage: not stated<br>Duration of intervention: 2 weeks. Note: It is not clear for how many days each boy received either of the methylphenidate doses or placebo<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>• Modified Conners' Scale Parent, daily, and Teacher ACR, 2 to 3 ratings per treatment condition. Daily reports of social and academic behaviour. Not stated who did the rating for these reports<br>• Swanson, Nolan and Pelham Scale, teacher-rated<br>• Abbreviated Conners' Rating Scale<br>• IOWA Conners' Teacher Rating Scale<br>**Non-serious adverse events**<br>• Rebound/Modified Conners' Scale, Parent, for rebound effect assessment<br>• Specific Behaviour Ratings by parent (5, specific individual problem behaviours, rated every night) |

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| **Notes** | Sample calculation: none<br>Ethics approval: no information<br>Funding/vested interest: no information<br>Any withdrawals due to adverse events: no<br>Author affiliations: University. No conflicting interests stated<br>**Comment from review authors**<br>1. Non-validated endpoints used. No definition (defined cutoff score on scales) of what the authors considered to be 'rebound'<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: not stated<br>Email correspondence with study authors: Emailed study authors to request additional information. Also asked whether this study includes the Pelham 1989 reference. No answer from study author, so we extracted data as from 2 different studies |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Order of drug condition for each child was randomly assigned over days |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Low risk | Child, parent, teacher and programme counsellors were blinded to the condition. Active medication and placebo were disguised in gelatin capsules and pre-packaged in individually dated envelopes |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not stated |
| Incomplete outcome data (attrition bias) | Unclear risk | Not stated<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Unclear risk | No protocol available |
| Vested interest bias | Low risk | Conflicts of interest: During the writing of this report, C. Johnston was supported by a Doctoral Fellowship from the Social Sciences and Humanities Research Council of Canada |

### *Kaplan 1990*

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| **Methods** | Three open trials, then a placebo-controlled, double-blind, cross-over study with 2 interventions<br>1. Methylphenidate<br>2. Placebo |

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| Participants | Number of participants screened: 6. Participants were randomly assigned to 1 of 2 possible drug condition orders<br>Number of participants followed up: 6 (all boys)<br>Number of withdrawals: 0. Three out-patients were studied in an open-label design<br>Diagnosis of ADHD: DSM-III (subtype not stated)<br>Age: mean 14.4 years (range 13 to 16)<br>IQ: mean 86 (range 76 to 97)<br>Methylphenidate naive: 5 (55%)<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic and in-patient ward<br>Comorbidity: aggressive conduct disorder (100%)<br>Comedication: yes; diphenhydramine 50 mg<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Meeting DSM-III criteria for both ADHD and aggressive conduct disorder<br>**Exclusion criteria**<br>1. Consent from parent or custodial social service agency<br>2. Psychosis or drug abuse history |
| Interventions | Participants were randomly assigned to 1 of 2 possible drug condition orders of 0.6 mg/kg, with 30 mg as a ceiling for methylphenidate and placebo<br>Mean methylphenidate dosage: 0.47 mg/kg<br>Administration schedule: twice a day, 8:00 AM and noon<br>Duration of each medication condition: 3 weeks<br>Washout before study initiation: 1 week<br>Medication-free period between interventions: 20 hours<br>Titration period: 1 week after randomisation<br>Treatment compliance: no information |
| Outcomes | **ADHD symptoms**<br>• Conners' Teacher Rating Scale: completed weekly by classroom teachers<br>• In addition, for in-patients, Conners' Rating Scale was completed weekly by the unit nurse<br>**Non-serious adverse events**<br>• Treatment Emergent Side Effect Scale: completed weekly by treating psychiatrists<br>• Dizziness, appetite loss and headache were reported in 3 of the 9 youngsters |

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| **Notes** | Sample calculation: no<br>Ethics approval: no information<br>**Comment from study authors**<br>1. As the result of an oversight, assignment to methylphenidate-first or placebo-first condition was made in the absence of a specific randomisation formula. Five of the 6 participants received placebo for the first condition and methylphenidate for the second condition<br>**Key conclusion of study authors**<br>1. Findings provide preliminary evidence of the efficacy of methylphenidate in reducing aggression among aggressive conduct-disordered adolescents also diagnosed with ADHD<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: March 2014. Emailed study author twice to request additional information but have not received a reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | High risk | As the result of an oversight, assignment to methylphenidate or placebo as the first condition was made in the absence of a specific randomisation formula. Five of the 6 participants received placebo for the first condition and methylphenidate for the second condition |
| Allocation concealment (selection bias) | Low risk | Assignment to order condition was determined with no knowledge of the particular participants involved; thus participants did not receive 1 condition or the other based on symptoms or any other systematic bias |
| Blinding of participants and personnel (performance bias) | Unclear risk | No information |
| Blinding of outcome assessment (detection bias) | Unclear risk | No information |
| Incomplete outcome data (attrition bias) | Unclear risk | In 2 cases, school vacation at the in-patient setting prevented teacher ratings from being obtained during 1 condition of the study. In those 2 instances, the decision was made to use Conners' ratings obtained from the unit nurse for both the condition for which no teacher ratings were provided and the condition for which teacher ratings were given; thus comparisons were consistent in terms of rater<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | No information |
| Vested interest bias | Unclear risk | No information |

### *Kelly 1989*

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| Methods | Double-blind, cross-over trial with 2 interventions<br>1. Methylphenidate<br>2. Placebo<br>Followed by long-term follow-up of 12 children out of 21 who continued to receive methylphenidate. Follow-up for an average of 16 months<br>**Phases**<br>1. Baseline<br>2. Cross-over study<br>3. Follow-up |
| Participants | **Regarding the cross-over trial**<br>Number of participants screened: not stated<br>Number of participants included: 26, but 5 children dropped out, 3 were removed by parents and 2 were disqualified because of a death in the family in 1 and a protocol procedural error in the other<br>Number of participants randomly assigned: 21 (18 boys, 3 girls)<br>Number of participants followed up: 21, plus 2 participants who had been withdrawn but returned later for follow-up<br>Number of withdrawals to follow-up: 0, but data for a few variables were not obtained for all participants<br>Diagnosis of ADHD: DSM-III<br>Age: mean 9.3 years (range 8 to 12)<br>IQ: mean 100.7<br>Methylphenidate naive: 100%<br>Ethnicity: White (62%), Hispanic/Oriental/Black (14%), mixed race (24%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: oppositional disorder (14%), enuresis (38%)<br>Comedication: not stated<br>Sociodemographics: 2-parent household (95%)<br>**Inclusion criteria**<br>1. ADHD diagnosis according to DSM-III<br>2. IQ > 80<br>3. Free of major health problems, neurological disorders or psychosis<br>**Exclusion criteria**<br>1. None stated |
| Interventions | Participants were randomly assigned to methylphenidate or placebo<br>Methylphenidate dosage: between 0.3 and 0.6 mg/kg/d in the short-term phase<br>Administration schedule: 2 time points a day<br>Duration of each medication condition: not stated<br>Washout before study initiation: from noon to the following morning (i.e. the next day)<br>Titration period: no |
| Outcomes | **ADHD symptoms**<br>1. Attention Deficit Disorder-Hyperactivity: Comprehensive Teacher Rating Scale: rated before diagnosis, at cross-over, at the conclusion of the short-term protocol and again during long-term follow-up<br>2. Conners' Parent Questionnaire: rated before diagnosis, at cross-over, at the conclusion of the short-term protocol and again during long-term follow-up |

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| **Notes** | Sample calculation: not stated<br>Ethics approval: yes<br>**Key conclusion of study authors**<br>1. Findings indicate that many pre-adolescents with ADHD exhibit low self esteem. Despite clinical response to medication, short-term improvement in self esteem may not occur; however, long-term, multi-modal management that includes medication does appear to improve self esteem<br>**Comment from review authors**<br>1. The data that we used in the review were derived from the cross-over period described<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: no<br>Email correspondence with study authors: January 2014. Study authors not able to provide us with further information |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | High risk | Child assigned in a double-blind, cross-over format to methylphenidate followed by placebo or placebo followed by methylphenidate |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Unclear risk | Double-blind |
| Blinding of outcome assessment (detection bias) | Unclear risk | Double-blind |
| Incomplete outcome data (attrition bias) | Low risk | Because data for a few variables were not obtained for all participants, a procedure for unbalanced analysis of variance was required and was accomplished by using the general linear model (GLM) procedure in the Statistical Analysis System (SAS)<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | Not stated |
| Vested interest bias | Unclear risk | CIBA Geigy Pharmaceuticals provided placebos<br>Conflicts of interest: no information |

### *Kent 1995*

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| **Methods** | Double-blind, cross-over trial with 3 interventions<br>1. Methylphenidate 10 mg<br>2. Methylphenidate 15 mg<br>3. Placebo<br>Phases: The first 2 doses (7:00 AM and noon) were unchanged from the open trial, whereas the 4:00 PM dose was 10 mg of methylphenidate, 15 mg of methylphenidate or placebo. Each of these 3 4:00 PM medication conditions was administered in random order during the 12-day period. Each medication condition was administered for a total of 4 days |

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| Participants | Number of participants screened: not stated<br>Number of participants included: 12 (11 boys, 1 girl). Participants were randomly assigned to different possible drug condition orders of methylphenidate and placebo<br>Number of participants followed up: not stated (but all 12 seem to appear in the results)<br>Number of withdrawals: not stated<br>Diagnosis of ADHD: DSM-III-R (subtype not stated)<br>Age: mean 9.0 years (SD 2, range 5.5 to 11.25)<br>IQ: not stated<br>Methylphenidate naive: 60%<br>Ethnicity: not stated<br>Country: USA<br>Setting: in-patient ward<br>Comorbidity: oppositional defiant disorder (25%), learning disability and oppositional defiant disorder (50%), conduct disorder (8%)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. In addition to fulfilling ADHD diagnostic criteria, patients were considered for the study only if they showed a beneficial response to an open trial of methylphenidate, as discussed below<br>**Exclusion criteria**<br>1. Major depressive disorder<br>2. Separation anxiety disorder<br>3. Tics or history of tics<br>4. Glaucoma<br>5. Psychosis or history of psychosis<br>6. Known hypersensitivity to methylphenidate |
| Interventions | Participants were randomly assigned to different possible drug condition orders of 10 mg or 15 mg methylphenidate and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: 7:00 AM, noon and 4:00 PM<br>Duration of each medication condition: 4 days<br>Washout before study initiation: none stated<br>Medication-free period between interventions: none<br>Titration period: Open titration of methylphenidate was accomplished within 14 days of the child's admission<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. Child Behavior Rating Form, rated by nursing staff: after each day shift and each evening shift<br>**Non-serious adverse events**<br>1. Sleep latency, sleep adequacy, food intake and weight: recorded by nursing staff |

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| **Notes** | Ethics approval: Informed consent for study participation was obtained from each child's parent or guardian. All procedures were approved by the study site's Human Subjects Research Review Committee<br>**Comment from study authors**<br>1. Patient population studied was particularly disturbed, and data were obtained in the context of in-patient treatment<br>**Key conclusions of study authors**<br>1. This study's findings show that children with ADHD derive substantial symptom reduction from methylphenidate administered in late afternoon, with no untoward effects on sleep. Therefore, t.i.d. should be considered for those children who exhibit ADHD symptoms in the evening<br>2. Adverse effects on sleep latency were not apparent in the sample overall<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; patients were excluded from consideration for study participation if they had known hypersensitivity to methylphenidate<br>Any withdrawals due to adverse events: none<br>Email correspondence with study authors: March 2014. Sent an email to study authors to request additional information but have not received a response |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Each of the 3 4:00 PM medication conditions was administered in random order during the 12-day double-blind cross-over period |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | The identity of each day's 4:00 PM dose was known only to the hospital pharmacist, until the child completed the 12-day protocol |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not stated |
| Incomplete outcome data (attrition bias) | Low risk | Results are provided for all 12 children<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Unclear risk | No protocol identified |
| Vested interest bias | Low risk | This work was supported by the John and Maxine Bendheim Fellowship and by the Leon Lowenstein Foundation<br>Conflicts of interest: not stated |

### *Kent 1999*

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| **Methods** | Cross-over trial with 3 interventions<br>1. Methylphenidate 0.3 mg/kg<br>2. Methylphenidate 0.6 mg/kg<br>3. Placebo<br>Phases: 3-week, double-blind, 2-way cross-over, long-term (≥ 12 months) follow-up |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 50 (38 boys, 12 girls). Participants were randomly assigned to different possible drug condition orders of methylphenidate and placebo<br>Number of participants followed up: 43<br>Number of withdrawals: 7<br>Diagnosis of ADHD: DSM-IV (subtype not stated)<br>Age: mean not reported (range 4 to 14 years)<br>IQ: "overall normal intelligence"<br>Methylphenidate naive: not stated<br>Ethnicity: not stated<br>Country: Canada<br>Setting: out-patient clinic<br>Comorbidity: depression (37%), anxiety (37%), learning disability (51%), conduct disorder (5%), "psychiatric disorder" (2%), Tourette's disorder (12%), "other" (23%)<br>Comedication: not stated<br>Sociodemographics: "Fifteen (30%) live in households that have a family income below the Canadian poverty line ($20,000/y)", 26 "rural", 9 "suburban", 14 "urban". 21 live with 1 biological parent, 24 live with both parents, 4 live with adoptive parents or "guardians"<br>**Inclusion criteria**<br>1. ADHD diagnosis<br>2. 4 to 14 years of age<br>3. English or French speaking<br>4. Living with caretakers with whom they had lived for longer than 6 months<br>5. Presence of a teacher who could evaluate the child in class<br>**Exclusion criteria**<br>1. History of significant developmental delay<br>2. Previous diagnosis of pervasive developmental disorder<br>3. Unwillingness of parents and/or school personnel to meet methylphenidate treatment requirements |
| Interventions | Participants were randomly assigned to different possible drug condition orders of 0.3 mg/kg methylphenidate and 0.6 mg/kg methylphenidate and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: Each new condition started on a Saturday morning (to allow parents' observation/evaluation on weekend). Capsules given at 8:00 AM and 12:00 PM. Conners' administered at baseline and on the last day of each week. A 30-minute semi structured follow-up interview was conducted ≥ 12 months after completion of the trial<br>Duration of each medication condition: 1 week<br>Washout before study initiation: not stated<br>Medication-free period between interventions: 12:00 PM to 8:00 AM the following day<br>Titration period: none initiated before/after randomisation<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. Conners' Parent Questionnaire: baseline and on the last day of each week<br>2. Conners' Teacher Questionnaire: baseline and on the last day of each week<br>**Non-serious adverse events**<br>1. Weekly reporting of side effects by parents and teachers. No use of standard side effects questionnaire |

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| **Notes** | Sample calculation: not stated<br>Ethics approval: yes; the Research Ethics Board of the IWK Grace Health Centre approved the protocol<br>**Comments from study authors**<br>1. "We found the MPT to be helpful, practical, and definitive for families of children with attention-deficit/hyperactivity disorder to making a decision about medication use"<br>2. "Regardless of the outcome, it was important for families to complete the MPT to understand, for their own child, the effect of methylphenidate on the child's behaviour and the presence of any side effects"<br>**Key conclusion of study authors**<br>1. "An 'N of 1' MPT was easily performed and permitted families to decide whether to use methylphenidate for long-term treatment of attention-deficit disorder or attention-deficit/hyperactivity disorder. Regardless of methylphenidate use or lack of use, the condition of all of these children was improved at follow-up"<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: not stated<br>Email correspondence with study authors: August 2013. We received additional information from study authors, but they were not able to provide the additional data that we requested |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "Once enrolled in the MPT, the non-blinded hospital pharmacist randomly assigned each child to a particular dosing schedule". "The capsules contained, in random order: placebo of the prescribed dose of methylphenidate (Ritalin) hydrochloride (0.3 mg/kg or 0.6 mg/kg)" |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Low risk | "Families (n = 50) with a child eligible for MPT were given 3 bottles of identical capsules". "The family, teacher, and physician were blinded for the order of medication" |
| Blinding of outcome assessment (detection bias) | Unclear risk | "At the end of each trial the code was broken. The physician evaluated this information and made a clinical inference about the degree of response each week" |
| Incomplete outcome data (attrition bias) | Unclear risk | Not stated |
| Selective reporting (reporting bias) | Unclear risk | Not stated |
| Vested interest bias | High risk | Not stated<br>Conflicts of interest: Study authors sponsored by Pharmaceutical Manufacturers' Association of Canada Studentship |

*Klorman 1990*

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| **Methods** | Cross-over trial with 2 interventions<br>1. Methylphenidate<br>2. Placebo<br>Phases: 2 |

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| Participants | Number of participants screened: not clear<br>Number of participants included: 48. Participants were randomly assigned to 1 of 1 dose of methylphenidate and placebo<br>Number of participants followed up: appears to have been 48<br>Number of withdrawals: not clear<br>Diagnosis of ADHD: DSM-III<br>Age: mean not stated (range 12 to 18 years)<br>IQ: mean 108.62<br>Sex: 42 boys, 6 girls<br>Methylphenidate naive: 46/48; 2 had brief trials in childhood<br>Ethnicity: Caucasian (n = 46)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: oppositional and conduct disorder (n = 24), oppositional not conduct disorder (n = 12), anxiety (n = 5), drug or alcohol abuse (n = 2), depression (n = 1)<br>Comedication: no<br>Sociodemographics: double- or single-parent family, predominantly middle class (mean Hollingshead socioeconomic status score of 48.8 (i.e. social class II))<br>**Inclusion criteria**<br>1. Participants 12 to 18 years of age without previous stimulant therapy referred for evaluation of response to stimulants from 1984 to 1988<br>**Exclusion criteria**<br>1. CNS involvement<br>2. Childhood autism<br>3. Psychosis<br>4. Uncorrected visual or auditory problems<br>5. IQ < 80 |
| Interventions | Participants were randomly assigned to 3 weeks of methylphenidate hydrochloride and placebo<br>Mean methylphenidate dosage: 35.21 mg (± 5.94 (SD)). Range 15 mg (2 daily doses) to 40 mg (3 daily doses)<br>Administration schedule: Doses were gradually increased at the end of the first and second weeks<br>Washout before study initiation: not described<br>Titration period: after randomisation<br>Treatment compliance: not described |
| Outcomes | **ADHD symptoms**<br>1. Abbreviated Conners' Hyperactivity Questionnaire: rated by teacher and parent, weekly<br>2. IOWA Inattention/Overactivity and Aggression Scales: rated by teacher and parent, weekly<br>Mean parent- and teacher-reported Conners' hyperactivity and inattention scores were graphed but SD values were not. Also, the paper did not refer to measures of impulsivity or total scores. We could not use these data in our meta-analyses because values were missing and study authors were not able to provide supplemental data on this outcome<br>**Non-serious adverse events**<br>1. Side effects reported in Table 3: appetite loss; increased thirst, dry mouth, stomachaches, nausea, headaches, sleep problems, shakiness, crying, anger, unhappiness, sadness |

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| **Notes** | Sample calculation: not described<br>Ethics approval: not described<br>**Key conclusion of study authors**<br>1. These results support the continued effectiveness of stimulant therapy for attention deficit disorder in adolescence. However, the magnitude of clinical effectiveness reported was smaller than was previously found in younger patients<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: April 2014. We obtained supplemental information/data from study authors (Magnusson 2014a [pers comm]) |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Received information from study author (Magnusson 2014a [pers comm]) |
| Allocation concealment (selection bias) | Low risk | Received information from study author (Magnusson 2014a [pers comm]) |
| Blinding of participants and personnel (performance bias) | Low risk | "Substances were dispensed in capsules of identical appearance" (p 703) |
| Blinding of outcome assessment (detection bias) | Low risk | Parent and teacher ratings were used and participants were blinded to which capsule they were receiving |
| Incomplete outcome data (attrition bias) | Unclear risk | Not stated<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | Not stated |
| Vested interest bias | Low risk | National Institute of Mental Health (NIMH) grant MH38118<br>Conflicts of interest: no corporate affiliations declared |

### *Kolko 1999*

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| **Methods** | Randomised, placebo-controlled, cross-over trial with 2 possible drug interventions and placebo, as well as 2 possible psychological interventions<br>1. Methylphenidate at 0.3 mg/kg<br>2. Methylphenidate at 0.6 mg/kg<br>3. Placebo<br>and<br>1. Behaviour modification<br>2. No behavioural modification |

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| Participants | Number of participants screened: 70<br>Number of participants included: 22 (all boys). Participants were randomly assigned to different possible drug condition orders<br>Number of participants followed up: 16<br>Number of withdrawals: 6<br>Diagnosis of ADHD: DSM-III-R (subtypes not stated)<br>Age: mean 9.6 years (range 6.9 to 12.9)<br>IQ: not stated<br>Methylphenidate naive: not stated<br>Ethnicity: African American (75%)<br>Country: USA<br>Setting: "partial hospitalisation" summer treatment programme<br>Comorbidity: conduct disorder (44%), oppositional defiant disorder (56%), anxiety disorder (18.8%), major depressive disorder (11.5%), dysthymia (6%), intermittent explosive disorder (6%), developmental articulation disorder (6%), asthma (12.5%)<br>Comedication: not stated<br>Sociodemographics: Three lived with 1 or both parents, 6 lived with grandparents, 1 lived with an aunt, 4 lived with non-relatives, 2 lived with foster mother. 44% of families received welfare<br>**Inclusion criteria**<br>1. Not stated<br>**Exclusion criteria**<br>1. Not stated |
| Interventions | Participants were randomly assigned to different possible drug condition orders of 0.3 mg/kg and 0.6 mg/kg methylphenidate and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: 8:00 AM and 11:30 AM to 12.00 PM<br>Duration of each medication condition: 1 day. Each medication condition was administered once per week for a total of 6 days during the trial<br>Washout before study initiation: 2 weeks<br>Medication-free period between interventions: no<br>Titration period: none<br>Treatment compliance: not stated<br>Behavioural intervention: behaviour modification and no behaviour modification were alternated on a weekly basis for a total of 3 weeks per condition |
| Outcomes | **ADHD symptoms**<br>1. Abbreviated IOWA Conners' Rating Scale, which includes an Inattentive/Overactive subscale and an Oppositional Defiant subscale<br>**Non-serious adverse events**<br>1. Barkley Stimulant Side Effects Rating Scale. Adapted by changing the rating scale to include only 4 points rather than 9 points |

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| **Notes** | Sample calculation: not stated<br>Ethics approval: not stated<br>**Key conclusions of study authors**<br>1. Methylphenidate and behaviour modification had certain unique, main and incremental effects that extend findings supporting their combination and suggest that integrated studies should evaluate multiple dimensions of functioning in novel settings<br>2. Incorporation of other intervention components in combined treatments may be warranted to enhance clinical efficacy<br>**Comments from review authors**<br>1. Barkley Stimulant Side Effects Rating Scale was adapted by changing the rating scale to include only 4 points (rather than 9 points) after pilot-testing. Therefore, we cannot be sure whether the scale is still valid<br>2. Limitations: The number of participants studied was small, and only 22 of 70 screened met study eligibility criteria<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study author: January 2014. We were unable to obtain additional data (Nilausen 2014 [pers comm]) |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Each methylphenidate condition was administered once per week for a total of 6 days during the trial, and behaviour modification and no behaviour modification were alternated on a weekly basis, for a total of 3 weeks per condition. Thus, daily methylphenidate conditions were crossed with 2 weekly behavioural intervention conditions |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Low risk | It is stated: "MPH or placebo was placed in identical opaque capsules" |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not stated |
| Incomplete outcome data (attrition bias) | High risk | Not stated<br>Selection bias: exclusion of 2 participants with challenging behaviour |
| Selective reporting (reporting bias) | Unclear risk | No protocol available |
| Vested interest bias | Unclear risk | Not stated<br>Conflicts of interest: no information |

### *Kollins 2006 (PATS)*

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| **Methods** | Eight-phase, 70-week, multi-centre trial (phase III study) including<br>1. Screening: varying time<br>2. Uncontrolled parent training: 10 weeks<br>3. Baseline: 2 to 4 weeks<br>4. Open-label, safety lead-in: 1 week<br>5. Random-sequence, double-blind, placebo-controlled, cross-over titration: 5 weeks. Optional pharmacogenetics study simultaneously<br>6. Randomised, optimal dose, double-blind, placebo-controlled, parallel trial: 4 weeks<br>7. Open-label, uncontrolled maintenance: 10 months<br>8. Randomised, double-blind, placebo discontinuation: 6 weeks<br>If parents requested and clinicians agreed that participants were severely symptomatic, children could be moved directly into the medication phase that was concurrent with parent training. If participants did not tolerate the dosing in phase 4, they could enter the open-label maintenance phase if they tolerated lower doses (e.g. 1.25 mg, 2.5 mg). If they tolerated all doses except 7.5 mg, they were eligible to enter phase 5, the cross-over titration, with the planned week on a 7.5-mg dose replaced by an additional 5-mg week. After phase 5, cross-over: (1) If the child showed the greatest clinical benefit during 1 of the 5 weeks of the cross-over trial, with no room for improvement, the blind was broken and the child was randomly assigned to that methylphenidate dose or placebo in phase 6; (2) if the child was a placebo responder, phase 6 was skipped and the child was allowed to enter phase 7 while taking no medication and with monthly monitoring by the treating physician; (3) if a particular week was deemed best, with ongoing room for improvement, a 2-week double-blind trial of 7.5 mg and 10 mg t.i.d., each for 1 week, was implemented, and teacher and parent ratings and side effects data were subsequently blindly reviewed to determine the best dose; or (4) participants with no clinical benefit any week were not eligible to continue in phase 6 or 7 but were given 1-month follow-up and then were referred for community treatment |
| **Participants** | Number of participants screened: 1915<br>Number of participants included in the study: 303 (229 boys, 74 girls)<br>Number of participants who completed the last phase of the study: 8<br>Number of withdrawals during the study: 295<br>Diagnosis of ADHD: DSM-IV (combined (75%), hyperactive-impulsive (25%), inattentive (0%))<br>Age: mean 4.41 years (range not reported)<br>IQ: > 70 (mean 99.06)<br>Methylphenidate naive: 100%<br>Ethnicity: Caucasian (63%), African American (19%), Asian (2%), Hispanic or Latino (16%), American Indian or Alaskan Native (0.7%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder (52%), communication disorder (22%), elimination disorder (i.e. encopresis, enuresis; 8%), specific phobia (8%), anxiety disorder (8%), developmental co-ordination disorder (3%), conduct disorder (2%), pica (2%), adjustment disorder (1%), reactive attachment disorder (1%), obsessive-compulsive disorder (0.7%), sleepwalking disorder (0.3%)<br>Comedication: no<br>Sociodemographics: double-parent family (76%), single-parent family (18%), mean Hollingshead socioeconomic status 47.20 (SD 9.56)<br>**Phase 4, open-label, safety lead-in**<br>Number of participants included: 183<br>Numberof participants followed up: 169<br>Number of withdrawals: 12<br>Number of participants leaving the study phase and entering maintenance (phase 7): 2<br>**Phase 5, cross-over**<br>Number of participants included: 165 (122 boys, 43 girls) |

Number of participants followed up: 147

Number of withdrawals: 14

Number of participants leaving the study phase and entering maintenance (phase 7): 4
Diagnosis of ADHD: DSM-IV (combined (76%), hyperactive-impulsive (24%), inattentive (0%))

Age: mean 4.74 years (range 3 to 5.5)

IQ: > 70 (mean 97.93)

Methylphenidate naive: 100%

Ethnicity: Caucasian (63%), African American (18%), Asian (1%), Hispanic or Latino (18%), American Indian or Alaskan Native (0.6%)

Country: USA

Comorbidity: oppositional defiant disorder (55%), communication disorder (20%), elimination disorder (i.e. encopresis, enuresis; 8%), specific phobia (7%), anxiety disorder (10%), developmental co-ordination disorder (4%), conduct disorder (3%), pica (2%), adjustment disorder (0.6%), reactive attachment disorder (2%), obsessive-compulsive disorder (0.6%), sleepwalking disorder (0.6%)

Comedication: no

Sociodemographics: double-parent family (79%), single-parent family (21%), mean Hollingshead socioeconomic status 47.01 (SD 9.58)

**Phase 6, parallel**

Number of participants included: 114 (85 boys, 29 girls)

Number of participants randomly assigned: methylphenidate 61, placebo 53

Number of participants followed up: 77

Number of withdrawals: 1

Number of participants leaving the study phase and entering maintenance (phase 7): 36

Diagnosis of ADHD: DSM-IV (combined (75%), hyperactive-impulsive (25%), inattentive (0%))

Age: mean 4.76 years (range not reported)

IQ: > 70 (mean 97.45)

Methylphenidate naive: 100%

Ethnicity: Caucasian (65%), African American (17%), Asian (0.9%), Hispanic or Latino (17%), American Indian or Alaskan Native (0.9%)

Country: USA

Comorbidity: oppositional defiant disorder (53%), communication disorder (22%), elimination disorder (i.e. encopresis, enuresis; 7%), specific phobia (7%), anxiety disorder (11%), developmental co-ordination disorder (5%), conduct disorder (3%), pica (0.9%), adjustment disorder (0.9%), reactive attachment disorder (2%), obsessive-compulsive disorder (0.9%), sleepwalking disorder (0.9%)

Comedication: no

Sociodemographics: double-parent family (80%), single-parent family (19%), mean Hollingshead socioeconomic status 47.61 (SD 9.45)

**Phase 7, open-label maintenance**

Number of participants included: 140 (104 boys, 36 girls)

Number of participants followed up: 95

Number of withdrawals: 45

Diagnosis of ADHD: DSM-IV (combined (76.4%), hyperactive-impulsive (23.6%), inattentive (0%))

Age: mean 4.4 years

IQ: > 70

Methylphenidate naive: 100%

Ethnicity: Caucasian (65.0%), African American (17.1%), Asian (1.4%), Hispanic

(15.7%), American Indian (0.7%)

Country: USA

Comorbidity: oppositional defiant disorder (52.9%), communication disorder (19.3%), anxiety disorder (11.4%)

Comedication: no

Sociodemographics: double-parent family (81.4%), single-parent family (18.6%), mean Hollingshead socioeconomic status 47.2 (SD 9.5)

**Inclusion criteria**

1. 36 to 65 months (3 to 5.5 years)
2. DSM-IV criteria for ADHD, hyperactive/impulsive or combined subtype, on Parent Diagnostic Interview Schedule for Children, Fourth Edition, and clinical interview by experienced clinician; symptoms were required to be present for a minimum of 9 months
3. Age- and sex-adjusted T score ≥ 65 on the Hyperactive-Impulsive subscale of Conners' Parent and Teacher Rating Scales
4. Score < 55 on the Children's Global Assessment of Functioning Scale
5. IQ > 70 as on the Differential Abilities Scale; children scoring < 70 were considered for inclusion if their composite score from the Vineland Adaptive Behavior Scale was > 70
6. Enrolled in some type of day programme: day care, pre-school, nursery school, kindergarten, for ≥ 2 half-days/wk. School-type programme, in which class included ≥ 8 same-age peers; if children had been expelled from an eligible programme in the 3 months before screening, they could be considered for enrolment
7. Teachers willing to complete rating scale
8. Residing with primary caretaker for ≥ 6 months before screening
9. Patients and parents willing to attend all visits required by the study
10. Otherwise generally healthy, and systolic and diastolic blood pressure below 95th percentile for age and sex
11. Stimulant-naive

**Additional inclusion criteria for phase 4, open-label lead-in**

1. Not showing substantial ADHD improvement after parent training (phase 2) (continued impairment, operationalised as < 30% reduction on Conners' Parent Rating Scale or Conners' Teacher Rating Scale, or a rating of less than "improved" by at least 2 of the 3 raters (parent, teacher, clinician) completing the Clinical Global Impressions Scale
2. Parental consent to a medication trial

**Additional inclusion criteria for phase 5, cross-over**

1. Tolerating the dosing in phase 4 (i.e. children with moderate to severe adverse events at doses < 5 mg in phase 4 were not eligible to continue)

**Exclusion criteria**

1. Children or their parent(s) could not understand or follow instructions given in the study
2. Evidence of moderate to severe adverse events or evidence of a much improved response to any dose of methylphenidate or another stimulant
3. > 5 weeks of exposure to ≥ 30 mg/d of methylphenidate or equivalent doses of other stimulants
4. Use of any other psychotropic medication or an investigational drug in the past 30 days; episodic use of sympathomimetic decongestants for the common cold under the study physician's supervision was allowed
5. History of motor or vocal tics or Tourette's syndrome
6. Major medical conditions that would interfere with involvement in a long-term study or could be affected negatively by methylphenidate
7. Current evidence of adjustment disorder, pervasive developmental disorders, autism, psychosis, significant suicidality or other psychiatric disorder, in addition to ADHD that requires treatment with additional medication
8. Evidence of current physical, sexual or emotional abuse
9. Living with anyone who currently abuses stimulants or cocaine
10. History of bipolar disorder in both biological parents

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All cases were presented to a cross-site panel of clinicians, and only patients for whom

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| | consensus indicated that all inclusion (and no exclusion) criteria were met could be enrolled |
| Interventions | **Phases 1 to 3**<br>Enrolment, parent training; baseline: no medical intervention<br>**Phases 4 to 8**<br>Medical intervention (short-acting, immediate-release methylphenidate)<br>**Phase 4, open-label, safety lead-in**<br>Titration: starting dose of 1.25 mg twice daily; increased to 7.5 mg 3 times daily<br>Duration: 1 week<br>Treatment compliance: not stated<br>**Phase 5, cross-over**<br>Randomly assigned sequence of doses of 1.25 mg, 2.5 mg, 5.0 mg or 7.5 mg immediate-release methylphenidate and placebo administered 3 times daily for a week<br>Medication-free period between interventions: none<br>Mean methylphenidate dose: not stated<br>Duration: 5 weeks<br>**Phase 6, parallel**<br>After a 24-hour medication washout, 4 weeks of randomly assigned treatment with a participant's optimal methylphenidate dose as determined in phase 5, or placebo<br>Mean methylphenidate dose: 14.22 mg/d, 0.7 mg/kg/d<br>Duration: 4 weeks<br>Treatment compliance: not stated<br>**Phase 7, open-label, maintenance**<br>Maintenance starting doses were based on the best dose decision from cross-over titration. Phase 5 placebo responders were maintained without medication for ≥ 4 weeks, unless their condition deteriorated, in which case open-label treatment could be initiated. For any participant whose condition deteriorated, the methylphenidate dose was gradually titrated for optimal response. The dosing regimen was adjusted to minimise some adverse events to 3 times daily (at breakfast, around noon after lunch and at 3:30 PM), 7 days a week<br>Mean methylphenidate dose: increased from 14.04 mg/d (0.71 mg/kg/d) at month 1 to 19.94 mg/d (0.92 mg/kg/d) at month 10<br>Duration: 10 months<br>Treatment compliance: not stated<br>**Phase 8, discontinuation**<br>Randomised, double-blind, placebo discontinuation trial, in which an abrupt medication replacement consisted of placebo for half of the children, while others continued on their best methylphenidate dose from the end of phase 7. Children returned to active medication if they met relapse criteria, in other words, Conners' Parent Rating Scale or Conners' Teacher Rating Scale scores on the Hyperactivity/Impulsivity Index > 1.5 SD above age- and sex-adjusted norms, or a clinician rating of 4 on the Clinical Global Impressions - Severity Scale<br>Duration: 6 weeks<br>Treatment compliance: not stated. Those who opted out of the double-blind phases would be allowed to continue on open-label maintenance therapy. This greatly reduced incentive for families to remain in the double-blind phases, especially if there was reason to suspect that a child had been randomly assigned to placebo |

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| Outcomes | **ADHD symptoms**<br>1. Conners', Loney and Milich Rating Scale, and Swanson, Kotkin, Agler, M-Flynn and Pelham Scale: teacher- and parent-rated weekly in phase 5<br>2. Swanson, Nolan and Pelham Scales, Fourth Edition, average of parent and teacher ratings: at the end of the last week (fourth) of phase 6<br>3. Conners' Parent Rating Scale, Conners' Teacher Rating Scale: rated by parents and teachers weekly in phase 8<br>**General behaviour**<br>1. Strengths and Weaknesses of Attention-Deficit/Hyperactivity Disorder Symptoms and Normal Behaviour Scale, Early Childhood Inventory: teacher- and parent-rated at baseline and at the end of phase 6<br>2. Child Behavior Checklist (home functioning)<br>3. Hillside Behaviour Rating Scale (school functioning)<br>**Quality of life**<br>1. Child Global Assessment Scale: completed only during non-randomised phases<br>**Serious adverse events**<br>1. Medication-related serious adverse events<br>**Non-serious adverse events**<br>1. Height and weight were measured without shoes or heavy clothes at each study visit. (Growth charts provided by the Centers for Disease Control and Prevention (CDC) were used to transform absolute units of measurement into Z-scores.) Laboratory tests were performed at each study visit<br>2. General clinician inquiry regarding the child's health problems at each study visit. Adverse events monitored by telephone, and parent- and teacher-rated in phase 4. Side Effects Rating Scale, parent-rated, weekly in phases 5, 6 and 8; monthly in phase 7. Side Effects Rating Scale, teacher-rated, weekly in phases 5 and 8, and in the last week of phase 6, as well as in first and tenth months of phase 7<br>3. Safety related to early and continued medication treatment evaluated at 6-year follow-up<br>4. Adverse Events Checklist was based on the Pittsburgh Side Effects Rating Scale. The 4-point (none, mild, moderate or severe) teacher-rated scale included the following: buccal-lingual movements; picking at skin or finger; lip or cheek chewing; other abnormal motor movements; worried, anxious appearance; dull, tired, listless appearance; headaches; stomachaches; crabby, irritable behaviour; tearful, sad, depressed behaviour; appetite loss; prone to crying; and uninterested in others with social withdrawal. The Parent Adverse Events Checklist also included trouble sleeping. Only adverse events rated as moderate or severe were counted as reportable in the open lead-in, titration and parallel phases of the study, whereas adverse events rated as mild, moderate or severe were reported from the maintenance phase<br>5. Blood pressure and pulse, at each study visit. Cardiovascular adverse events were based on age-adjusted normative values. Tachycardia was defined as 2 measurements of resting heart rate above 120 beats per minute (bpm) at the same visit. Hypertension was defined as 2 blood pressure readings at the same visit that were above the 95th percentile for age and sex (systolic or diastolic), ranging from 110/72 for 3-year-olds to 115/74 for 6-year-olds. Blood pressure was checked again within 7 to 14 days. If the reading remained above the cutoff limit, an adverse event for hypertension was reported. Hypertension was rated as mild if < 10 mmHg, moderate if 11 mmHg to 20 mmHg and severe if > 20 mmHg above the limit |
| Notes | Sample calculation: yes. Target sample size stated in the online protocol 165. Sample to be randomly assigned 120<br>Ethics approval: yes; by institutional review boards at each study site. The study was monitored by the Data and Safety Monitoring Board of the National Institute of Mental Health<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Comments from study authors (limitations)**<br>1. Design: The study included only immediate-release methylphenidate, not an extended-release preparation. The study may have included an order effect in the cross-over phase, particularly for children who were randomly assigned to receive |

higher doses first. The PATS protocol did not provide a stimulant-untreated clinical control group in non-controlled phases. Comparisons of height and weight before and after treatment were made against population norms (i.e. children without an ADHD diagnosis and methylphenidate-exposure). The follow-up period was not sufficient for evaluation of the critical issue of long-term effects of initial growth suppression observed in the first year of treatment

2. Dose: Doses used in the PATS were relatively low and homogeneous, and the high end of the proposed dose range was truncated. This may have masked dose-related effects
3. Population: The rigorous procedures for diagnosis of ADHD enhanced the validity of the diagnostic process at the expense of excluding some children likely to have met the conventional criteria for ADHD in other settings. Children who showed substantial ADHD improvement after parent training were not eligible for medication phases. The sample was too small for the medication to be declared safe for this age group. Failure to meet remission criteria may be caused by severity of ADHD symptoms, not by possible ineffectivity of methylphenidate in pre-schoolers with ADHD. A high attrition rate and differential attrition rates in the allocated groups were possibly due to a delayed study start, repeated consent procedures, an always available option to skip directly into maintenance and greater nervousness among parents about medication side effects in pre-schoolers. Parents' experience during the titration phase presumably heightened their awareness of behavioural differences associated with active and placebo medication
4. Data: missing data in general. Adverse event data entry procedures may have inflated adverse event rates. Parents were told when double-blind switches between the drug took place. This may have contributed to confounding of negative expectancy and reporting of adverse events
5. Exploratory moderator analyses of efficacy data from phase 5 (cross-over): No adjustments were made for multiple comparisons. Findings should be considered preliminary. The Diagnostic Interview Schedule for Children, Fourth Edition, Parent Version, has not been validated in pre-school children. Sample sizes across different moderator categories/subgroups were relatively small. Data on compliance were missing

**Key conclusions of study authors**

1. Phase 5 (cross-over): Immediate-release methylphenidate, delivered in 2.5-mg, 5-mg and 7.5-mg doses t.i.d., produced significant reductions in ADHD symptom scale scores in pre-schoolers compared with placebo, although effect sizes (0.4 to 0.8) were smaller than those cited for school-aged children taking the same medication
2. Pharmacogenetics study in phase 5 (cross-over): Emerging evidence suggests the potential for understanding individual variability of responses to and side effects of ADHD medications through the study of genetics, although additional research is required before these findings can be proven to have clinical utility
3. Exploratory moderator analyses of efficacy data from phase 5 (cross-over): Of the 14 variables examined as potential moderators, only 1 (number of concurrent comorbid disorders) served as a moderator of methylphenidate dose response. In pre-schoolers with ADHD, the presence of no or 1 comorbid disorder (primarily oppositional defiant disorder) predicted a large treatment response at the same level as has been found in school-aged children, and 2 comorbid disorders predicted moderate treatment response; whereas the presence of ≥ 3 comorbid disorders predicted no treatment response to methylphenidate
4. Phase 6 (parallel): Medication effects varied by informant and outcome measure. Parent measures and teacher scores on the Strengths and Weaknesses of Attention-Deficit/Hyperactivity Disorder Symptoms and Normal Behaviour Scale did not differentially improve with methylphenidate. Parent-rated depression (P value < 0.02) and dysthymia (P value < 0.001) on the Early Childhood Inventory worsened with methylphenidate, but scores were not in the clinical range. Significant medication effects were found on the clinician Clinical Global Impressions - Severity Scale (P value < 0.0001) and in teacher ratings on the Social Competence Scale (P value < 0.03). Pre-schoolers with ADHD treated with methylphenidate for 4 weeks improve in some aspects of functioning. Additional improvements might require longer treatment, higher doses and/or intensive behavioural treatment in combination with medication
5. Phase 7 (maintenance): With careful monitoring and a gradual medication dose increase, most pre-schoolers with ADHD maintained improvement during long-term immediate-release methylphenidate treatment. Variability in effective and tolerated dosing was substantial

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| | 6. Entire study duration<br>a. Adverse events during the study: 11% of pre-schoolers discontinued treatment because of intolerable methylphenidate adverse events. Of the serious adverse events reported, 1 occurred at baseline, 2 at lead-in, 3 in titration, 1 in parallel and 1 in maintenance. Only 1 was possibly related to methylphenidate<br>b. Growth during the study: Average relative size at baseline was significantly greater than 0 for z height and z weight, indicating greater than expected height (by 2.04 cm) and weight (by 1.78 kg) for participants. During treatment, slopes were significantly less than 0 for z height and z weight, indicating reduction in growth rates. For 95 children who remained on medication, annual growth rates were 20.3% less than expected for height (-1.38 cm/y) and 55.2% less (-1.32 kg/y) for weight. Risks of reduced growth rates should be balanced against expected benefits when pre-school-aged children are treated with stimulant medication<br>Withdrawals due to adverse events: number of withdrawals due to adverse events during medication phases: 21 (i.e. 11%)<br>Number of participants leaving study phase and entering maintenance (phase 7): 4<br>Email correspondence with study authors: June 2014. We obtained supplemental information/data from the study authors |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | 1. Phase 5 (cross-over): Randomisation was done centrally at the co-ordinating site, using a computerised stratified randomisation, a 1:1:1:1 starting dose allocation ratio and a randomised, balanced, cross-over protocol designed to avoid order effects<br>2. Phase 6 (parallel-group): A second randomisation to active methylphenidate or to placebo was performed before entry into the parallel-design, placebo-controlled phase<br>3. Phase 8 (discontinuation): Centralized randomisation used a computer programme; each child was allocated 1:1 to continuing methylphenidate or switching to placebo under double-blind conditions |
| Allocation concealment (selection bias) | Low risk | 1. Phase 5 (cross-over): central randomisation using a computer programme<br>2. Phase 6 (parallel-group): central randomisation using a computer programme<br>3. Phase 8 (discontinuation): central randomisation using a computer programme |
| Blinding of participants and personnel (performance bias) | Low risk | 1. Phase 5 (cross-over): double-blind. Placebo pills were identical to pills containing active medication capsules<br>2. Phase 6 (parallel-group): double-blind. Placebo pills were identical to pills containing active medication capsules<br>3. Phase 8 (discontinuation): double-blind. Placebo pills were identical to pills containing active medication capsules |
| Blinding of outcome assessment (detection bias) | Low risk | 1. Phase 5 (cross-over): double-blind. Except in emergencies, clinicians remained blind to dose sequences. Blinding was maintained for primary dependent measures until after the best dose was determined, or as needed. Parent and teacher dose-response rating scale graphs were prepared and were blindly evaluated by 2 study clinicians<br>2. Phase 6 (parallel-group): double-blind. Except in emergencies, clinicians remained blind to dose sequences. Blinding was maintained for primary dependent measures until after the best dose was determined, or as needed. Parent and teacher dose-response rating scale<br>3. Phase 8 (discontinuation): double-blind |

| Bias | Authors' judgement | Support for judgement |
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| Incomplete outcome data (attrition bias) | Low risk | 1. Phase 5 (cross-over): All analyses were run using the ITT principle (i.e. each observation obtained for the child was used in the analysis, including those from children who entered each of the 2 phases under consideration and did not complete the phase)<br>2. Phase 6 (parallel-group): All analyses were run using the ITT principle (i.e. each observation obtained for the child was used in the analysis, including those from children who entered each of the 2 phases under consideration and did not complete the phase)<br>3. Phase 8 (discontinuation): ITT |
| Selective reporting (reporting bias) | Low risk | 1. Phase 5 (cross-over): outcome measures reported in accordance with the published protocol<br>2. Phase 6 (parallel-group): outcome measures reported in accordance with the published protocol<br>3. Phase 8 (discontinuation): not relevant |
| Vested interest bias | High risk | 1. Phase 5 (cross-over): sponsored by the National Institute of Mental Health, Columbia/New York State Psychiatric Institute, Johns Hopkins University, Columbia University, University of California Irvine, Duke University Medical Center, New York University Child Study Center and University of California Los Angeles, Arizona Institute of Mental Health Research to J.K.G. Generic methylphenidate was purchased by grant funds<br>2. Phase 6 (parallel-group): sponsored by the National Institute of Mental Health, Columbia/New York State Psychiatric Institute, Johns Hopkins University, Columbia University, University of California Irvine, Duke University Medical Center, New York University Child Study Center and University of California Los Angeles, Arizona Institute of Mental Health Research to J.K.G. Generic methylphenidate was purchased by grant funds.<br>3. Phase 8 (discontinuation): sponsored by the National Institute of Mental Health, Columbia/New York State Psychiatric Institute, Johns Hopkins University, Columbia University, University of California Irvine, Duke University Medical Center, New York University Child Study Center and University of California Los Angeles, Arizona Institute of Mental Health Research to J.K.G. Generic methylphenidate was purchased by grant funds<br>**Conflicts of interest**<br>1. Phase 5 (cross-over): Multiple study authors had relationships with several pharmaceutical companies for the period 2000 to 2007<br>2. Phase 6 (parallel-group): Multiple study authors had relationships with several pharmaceutical companies for the period 2000 to 2007. Placebo responders in phase 5 were excluded from phase 6. Participants with no clinical benefit any week were excluded from phase 6 (methylphenidate non-responders)<br>3. Phase 8 (discontinuation): Multiple study authors had relationships with several pharmaceutical companies for the period 2000 to 2007 |

*Konrad 2004*

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| Methods | Double-blind, placebo-controlled, within-participant trial of cross-over design, lasting 6 days with 2 possible drug interventions and placebo<br>1. Methylphenidate 0.25 mg/kg (low dose)<br>2. Methylphenidate 0.5 mg/kg (high dose)<br>3. Placebo<br>The order of drug conditions was randomly assigned, with the restriction that higher doses should never be administered after placebo |

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| Participants | Number of participants screened: not stated<br>Number of participants included: 60 (44 boys, 16 girls)<br>Number of participants randomly assigned: low-dose methylphenidate 60; high-dose methylphenidate 60; placebo 60<br>Number of participants followed up: 60 in each arm<br>Number of withdrawals: not stated for each arm<br>Diagnosis of ADHD: DSM-IV (combined 47 (78%), inattentive 13 (22%))<br>Age: mean 10.8 years (SD 1.6, range 8 to 12)<br>IQ: mean 97.4 (SD 10.7, range not stated)<br>Methylphenidate naive: 100%<br>Ethnicity: not stated<br>Country: Germany<br>Setting: out-patient clinic and in-patient ward<br>Comorbidity: oppositional defiant disorder (n = 6; 10%), conduct disorder (n = 18; 30%), anxiety (n = 12; 18%), dyslexia (n = 19; 32%)<br>Comedication: no<br>Sociodemographics: not stated. No significant differences in baseline demographics were noted between the 2 groups<br>**Inclusion criteria**<br>1. Only children without a prior history of stimulant treatment were included in the study protocol<br>**Exclusion criteria**<br>1. General IQ < 80 (Wechsler Intelligence Scale for Children, Third Edition)<br>2. Any potentially confounding diagnoses such as psychosis, mania, major depression, substance abuse, pervasive developmental disorders, receptive language disorders<br>3. Use of any kind of additional medication (including selective serotonin reuptake inhibitors or anticonvulsants) |
| Interventions | Participants were randomly assigned to "low-dose" methylphenidate (0.25 mg/kg), "high-dose" methylphenidate (0.5 mg/kg) and placebo<br>Mean methylphenidate dosage: 9.2 mg (SD 2.2) for low-dose group (0.25 mg/kg), 18.4 mg (SD 5.4) for high-dose group (0.5 mg/kg)<br>Administration schedule: Medication was given between 7:00 AM and 8:00 AM for 6 days. "Cognitive testing began 60 minutes after medication ingestion and lasted 80 minutes". The order of drug conditions was randomly assigned, with the restriction that higher doses should never be administered after placebo. Thus, 11 orders were possible for the 6-day procedure as a whole, and 6 orders were possible for the sequence of the 3 neuropsychological assessments. Children were assigned in equal numbers to the 6 orders<br>Duration of intervention: 6-day intervention<br>Titration period: 1 week of 0.3 mg/kg methylphenidate for each participant "to ascertain tolerance"<br>Treatment compliance: not stated |

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| Outcomes | **ADHD symptoms**<br>1. Primary outcomes<br>a. German Teacher's and Parental Report on ADHD symptoms (Fremdbeurteilungsbogen für Hyperkinetische Störungen)<br>b. Parental questionnaire on ADHD symptoms (Diagnostiksystem für Psychische Störungen im Kindes- und Jugendalter nach ICD-10 und DSM-IV)<br>c. Child Behavior Checklist<br>2. Specific attentional outcome measures<br>a. Baseline speed: assessed with a simple reaction time task<br>b. Sustained attention: involved the continuous and consecutive presentation of 50 series of 12 different dot patterns (600 signals)<br>c. Focused attention: Four letters were presented simultaneously, and the child was instructed to respond with the "yes" key to 1 target letter, but only if this occurred in 1 of the relevant diagonal positions<br>d. Divided attention: dual task that combined optic and acoustic discrimination tasks<br>e. Stop-Signal paradigm: The "go" task in our stop-signal task was a choice reaction task in which an unidentified flying object (UFO) appeared to the left or right of a fixation cross<br>f. Visual set-shifting: Task consisted of 3 parts |
| Notes | Sample calculation: not stated<br>Ethics approval: yes; "the study was approved by the Medical Ethical Committee of the University Hospital of Aachen"<br>**Comments from study authors**<br>1. The present study investigated effects of day-to-day medication on attentional functions, which might differ from dose-dependent effects in the long run<br>2. Our study did not include a third methylphenidate dose, which would have allowed additional study of dose-response curves for higher doses of methylphenidate<br>**Key conclusions of study authors**<br>1. Results indicate that attentional functions are influenced differentially by methylphenidate; intensity-dimension functions are best influenced by higher doses, executive functions by moderate doses and selectivity-dimension functions by variable doses<br>2. Divergent results from behaviour rating scales and from attentional paradigms emphasise that clinicians have to decide what constitutes an appropriate clinical response<br>3. A more comprehensive assessment of attention may help to reveal an individually optimal dose for the treatment of attentional dysfunction<br>**Comment from review authors**<br>1. This study focuses on aspects of attention in relation to methylphenidate<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: unclear; only children without a prior history of stimulant treatment were included in the study protocol<br>Any withdrawals due to adverse events: not stated<br>Email correspondence with study authors: January 2014. We sent an email to the study author to request additional information but have not received a reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Within the 6-day protocol, the order of drug conditions was randomly assigned, with the restriction that higher doses should never be administered after placebo |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Low risk | "The active medication and placebo were prepared by a study protocol physician who was not involved in the assessment. All capsules were identical opaque gelatin capsules and were administered in a double-blinded manner. Capsules containing placebo (lactose) or 0.25 mg/kg or 0.5 mg/kg doses of methylphenidate were prepared for each participant" |
| Blinding of outcome assessment (detection bias) | Low risk | As above |
| Incomplete outcome data (attrition bias) | High risk | "Due to computer problems, data for four children in one task in one condition were missing. As recommended by Tabachnik and Fidell (1996), these data were replaced by the average of the group per condition"<br>Selection bias: yes; before testing, all children were given 0.3 mg/kg methylphenidate each day for ≥ 1 week to ascertain tolerance |
| Selective reporting (reporting bias) | Unclear risk | Not stated |
| Vested interest bias | Low risk | This research was funded by the German Society for the Advancement of Scientific Research (DFG grant KFO112)<br>Conflicts of interest: none declared |

### *Konrad 2005*

| Methods | Cross-over trial with 2 interventions<br>1. Methylphenidate (low and high doses)<br>2. Placebo |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 44 (37 boys (84%), 7 girls (16%))<br>Number of participants followed up: 44<br>Number of withdrawals: not stated<br>Diagnosis of ADHD: DSM-IV (combined type 100%)<br>Age: mean 10.3 years (SD 1.9, range 8 to 12)<br>IQ: mean 98.1<br>Methylphenidate naive: not stated<br>Ethnicity: not stated<br>Country: Germany<br>Setting: in-patient ward<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. ADHD diagnosis using multiple measures and observation in playroom, etc.<br>2. Children were included only if they also met criteria for ADHD diagnosis on teachers' rating scale<br>**Exclusion criteria**<br>1. General IQ < 80 (Wechsler Intelligence Scale for Children, Third Edition)<br>2. Any pervasive developmental disorders, receptive language disorders, visual impairments<br>3. Any kind of additional medication (including selective serotonin reuptake inhibitors (SSRIs) or anticonvulsants) |
| Interventions | Participants were randomly assigned to 1 of 6 possible drug condition orders of 0.25 mg/kg (low dose) or 0.5 mg/kg (high dose) methylphenidate and placebo<br>Mean methylphenidate dosage: 9.4 mg (SD 2.3) for the 0.25-mg/kg dose; 18.6 mg (SD 5.3) for the 0.50-mg/kg dose<br>Administration schedule: not stated<br>Time points: not stated<br>Duration of each medication condition: 2 days<br>Washout before study initiation: not stated<br>Medication-free period between interventions: no<br>Titration period: Before testing, all children were given 0.30 mg/kg methylphenidate each day for ≥ 1 week to ascertain tolerance<br>Treatment compliance: not stated. Within the 6-day protocol, the order of drug conditions was randomly assigned, with the restriction that the high dose never occurred right after placebo |
| Outcomes | **ADHD symptoms**<br>1. Primary outcomes<br>a. German Teachers' Report on ADHD Symptoms (Fremdbeurteilungsbogen für Hyperkinetische Störungen) of the Parental Questionnaire of ADHD symptoms (Diagnostiksystem für Psychische Störungen im Kindes und Jugendalter nach ICD-10 und DSM-IV). Sum scores were calculated separately for both symptom scales (hyperactive-impulsive symptoms and inattentive symptoms) |

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| **Notes** | Sample calculation: not stated<br>Ethics approval: yes; informed parental consent was obtained for all participants, and the study was approved by the Medical Ethical Committee of the University<br>**Key conclusions of study authors**<br>1. Trend tests revealed linear effects of methylphenidate dose on actigraph data in the test session (P value = 0.02) and at school (P value = 0.001), as well as on sustained attention (P value < 0.001); inhibitory control showed a quadratic dose-response curve (P value < 0.001)<br>2. Multi-variate regression analyses revealed that changes in both hyperactive-impulsive symptoms (28%) and inattentive symptoms (23%) could be explained by objective changes in motor activity. Thus, for clinical practice, it should be taken into account that behaviour ratings of ADHD symptoms seemed to be predominantly influenced by changes in motor activity<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; before testing, all children were given 0.30 mg/kg methylphenidate each day for ≥ 1 week to ascertain tolerance<br>Any withdrawals due to adverse events: not stated<br>Email correspondence with study author: July 2015. Email sent to study author to ask for additional information, but we have received no reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Within the 6-day protocol, the order of drug conditions was randomly assigned, with the restriction that the high dose never was given immediately after placebo |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Low risk | Active medication and placebo were prepared by a study protocol physician who was not involved in the assessment. All capsules were identical opaque gelatin capsules and were administered in a double-blind manner |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not stated |
| Incomplete outcome data (attrition bias) | Unclear risk | Not stated<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Unclear risk | Not stated |
| Vested interest bias | Low risk | Funding for this research was provided through a grant from the German Research Foundation (DFG grant: KFO112–TP5)<br>Conflicts of interest: none declared |

### *Leddy 2009*

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| **Methods** | Nine-week, randomised, controlled trial (RCT), cross-over design, with 2 interventions<br>1. Methylphenidate<br>2. Placebo<br>Phases: 1 |

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| Participants | Number of participants screened: 154<br>Number of participants included: 58 (sex not stated). Participants were randomly assigned to 1 of 3 possible drug condition orders<br>Number of participants followed up: not stated<br>Number of withdrawals: not stated<br>Diagnosis of ADHD: DSM-IV (combined (95%), hyperactive-impulsive (2%), inattentive (3%))<br>Age: mean not stated (range 6 to 12 years)<br>IQ: > 80<br>Methylphenidate naive: 19%<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic (summer treatment programme)<br>Comorbidity: oppositional defiant disorder (52%), conduct disorder (10.5%)<br>Comedication: no<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. 6 to 12 years of age<br>2. ADHD (DSM-IV)<br>3. IQ ≧ 80<br>4. Symptoms positive for both Disruptive Behavior Disorders Rating Scale and Diagnostic Interview Schedule for Children<br>5. Impairment in 2 settings (Impairment Rating Scale)<br>**Exclusion criteria**<br>1. Seizures/serious neurological problem<br>2. Pervasive developmental disorder, schizophrenia or other psychotic disorder<br>3. Necessity of psychotropic medication for treatment of a comorbid disorder |
| Interventions | Participants were randomly assigned to different possible drug condition orders of 0.15 mg/kg (t.i.d.) methylphenidate, 0.3 mg/kg (t.i.d.) methylphenidate, 0.6 mg/kg (t.i.d.) methylphenidate and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: 3 time points<br>Duration of each medication condition: 12 days for placebo, methylphenidate 0.15 mg and methylphenidate 0.3 mg; 9 days for methylphenidate 0.6 mg<br>Washout before study initiation: not stated<br>Medication-free period between interventions: no<br>Titration period: not stated<br>Treatment compliance: not stated |
| Outcomes | **General behaviour**<br>1. Disruptive Behavior Disorders Rating Scale<br>**Non-serious adverse events**<br>1. Pittsburgh Side Effects Rating Scale |

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| **Notes** | Sample calculation: not stated<br>Ethics approval: yes<br>**Key conclusion of study authors**<br>1. "among children with ADHD, those with DA-related genotypes associated with greater brain DA signalling, DAT SLC6A3 9/9, and DRD2 A2/A2, showed a greater suppression of lunch meal intake as MPH dose increased in comparison to children with DA genotypes associated with lower brain DA signaling"<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: not stated<br>Any withdrawals due to adverse events: not stated<br>Email correspondence with study author: June 2014. Emailed the study author to ask for raw data regarding side effects, data from the Disruptive Behavior Disorders Rating Scale and other data. Study author responded to say he did not have them (Holmskov 2014 [pers comm]) |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "Drug dose varied daily on a randomized basis and included four conditions (...)" |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Unclear risk | "Double-blind" |
| Blinding of outcome assessment (detection bias) | Unclear risk | "Double-blind" |
| Incomplete outcome data (attrition bias) | Unclear risk | No information |
| Selective reporting (reporting bias) | Unclear risk | No protocol identified |
| Vested interest bias | High risk | Conflicts of interest: Dr. Waxmonsky has served on the Speakers' Board for Novartis, received an honorarium from Shire and received research support from Shire and Eli Lilly. Dr. Erbe has received educational and research support from Genzyme Corporation. Dr. Pelham was paid an honorarium by Shire Pharmaceuticals |

### *Lehmkuhl 2002*

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| **Methods** | Four-week, randomised, double-blind, parallel trial with 2 arms<br>1. Sustained-release methylphenidate 20 mg to 60 mg<br>2. Placebo |

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| Participants | Number of participants screened: 102<br>Number of participants included: 85 (75 boys, 10 girls)<br>Number of participants randomly assigned: methylphenidate 43, placebo 42<br>Number of participants followed up: methylphenidate 40, placebo 38<br>Number of withdrawals: methylphenidate 3, placebo 4<br>Diagnosis of ADHD: DSM-IV (combined (74.1%), hyperactive-impulsive (0%), inattentive (24.7%), unspecified (1.2%))<br>Age: mean 9.8 years (range 6 to 15)<br>Mean IQ: methylphenidate 104.8, placebo 102.7 (range 85 to 146)<br>Methylphenidate naive: 25 (29.4%)<br>Ethnicity: German (82), other (3)<br>Country: Germany<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder (51.8%), conduct disorder (9.4%), unspecified conduct disorder (3.5%), dysthymia (1.2%)<br>Comedication: yes (n = 4)<br>Sociodemographics: not stated. The 2 groups were homogeneous in terms of sex distribution, school type, school class and nationality (At baseline, SERS-D ratings for disturbed sleep, nightmares, sadness, weepiness, anxiety, drowsiness and nervous twitching were far more pronounced in group 1 than in group 2. These initial differences – except for sadness – levelled out during the 4-week trial period)<br>Additional conduct disorders are less frequent in the group treated with medication (25 vs 30 participants), but this slight difference is not significant (Fisher's exact test, P value = 0.26)<br>**Inclusion criteria**<br>1. DSM-IV diagnosis of ADHD, verified against the ADHD Diagnostic Checklist from the Diagnostic System for Mental Disorders in Childhood and Adolescence, as per ICD-10 and DSM-IV<br>2. According to the class teacher, occurrence of considerable ADHD symptoms over the previous 3 school days (provided the mean score on the aggregate Fremdbeurteilungsbogen für Hyper kinetische Störunge rating scale was > 1.0)<br>3. Patients between 6 and 16 years of age<br>4. Attendance at an elementary or secondary school<br>5. IQ > 85<br>6. Body weight > 20 kg<br>**Exclusion criteria**<br>1. Diagnosis of depression or anxiety<br>2. Tics or Tourette's syndrome or family occurrence of tic disorder<br>3. Pervasive developmental disorder<br>4. Psychosis<br>5. History of seizures or evidence on the EEG of risk of seizures<br>6. Pre-treatment of patients with methylphenidate or other psychostimulants up to 3 weeks before the study<br>7. Lack of knowledge of the German language of the patient or legal guardian |

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| Interventions | Participants were randomly assigned to sustained-release methylphenidate or placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: once daily after breakfast<br>Duration of intervention: 4 weeks<br>Titration period: weekly dose titration initiated after randomisation. Initially, two 5 mg methylphenidate/placebo tablets/d for 2 days, then 20 mg (1 sustained-release methylphenidate capsule/placebo) dosage increased to 40 mg and 60 mg, depending on weight and course of symptoms. Titration up to 40 mg and 60 mg modified-release methylphenidate was possible in the second and third weeks of treatment, respectively (20 kg to 30 kg, maximum 20 mg modified-release methylphenidate; 31 kg to 50 kg, maximum 40 mg modified-release methylphenidate; < 50 kg, maximum 60 mg modified-release methylphenidate)<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. Moderation of ADHD symptoms according to teacher rating on the basis of the Fremdbeurteilungsbogen für Hyperkinetische Störungen (aggregate rating scale), an ADHD response-symptom checklist for observers based on ICD-10 and DSM IV<br>2. Fremdbeurteilungsbogen für Hyper kinetische Störungen (aggregate rating scale) rated by observers, parents and teachers: rated each week (teacher rated in the morning, parents in the afternoon)<br>3. Conners' abbreviated questionnaire, teacher and parent/guardian rated: rated each week (teacher rated in the morning, parents in the afternoon)<br>**Serious adverse events**<br>1. One serious adverse event - appendicitis - occurred in the methylphenidate group. A relationship between the adverse event and the medication product is considered unlikely by the study authors<br>**Non-serious adverse events**<br>1. Adverse events, documented by the investigating physician each week<br>2. Vital parameters, assessed each week<br>3. Blood analyses, assessed each week<br>4. EEG, performed at screening and at the end of the study - no remarkable changes were found during the study<br>5. Physical and neurological examinations, performed at screening and at the end of the study - no remarkable changes were found during the study<br>6. Barkley Side Effect Rating Scale-D, rated by parents and participants, time point not stated<br>7. Neurological psychiatric adverse events were classified as follows<br>a. Neurological disorders (e.g. headaches, disturbed sleep)<br>b. Psychiatric disorders (e.g. sadness, aggressiveness) |

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| Notes | Sample calculation:yes<br>Ethics approval: approved by local university ethics committees<br>**Comments from study authors**<br>1. Participant and parent observations differ to some extent from investigating physicians' documentation of adverse events. Differences in disturbed sleep, sadness and weepiness between the 2 medication groups during week 1 thus seem more likely to be the result of initial differences and homogeneities before the start of the trial, as they improve over the course of the trial under treatment with methylphenidate<br>2. No clinically relevant changes on laboratory measures before and after the study<br>**Key conclusions of study authors**<br>1. This trial demonstrated clinically relevant and statistically significant benefits of medication over placebo during 4-week therapy<br>2. Lehmkuhl 2002: In both the confirmatory analysis (change in teacher-rated aggregate Fremdbeurteilungsbogen für Hyper kinetische Störungen rating scale) and all secondary hypotheses of efficacy, medication 1 (methylphenidate) always proved far more effective than medication 2 (placebo). This effect is clinically relevant. Under medication 1, however, adverse events were considerably more frequent and severe<br>3. Sinzig 2007 (in Lehmkuhl 2002): Long-acting methylphenidate is effective in the treatment of oppositional defiant disorder and aggressive behaviour, especially with milder symptoms. Expected correlation between impulsivity and aggressiveness could be confirmed<br>**Comments from review authors**<br>1. Lemkuhl 2002 and Döpfner 2003 (in Lehmkuhl 2002): Only one review author, who knew German, has extracted data from these 2 articles. Two review authors assessed the other 3 articles and extracted data<br>2. No one chose to withdraw, but because of administrative mistakes, comedication, etc., participants were taken out per protocol<br>3. Unpublished data from this study were received from HB Pharma<br>Any withdrawals due to adverse events: yes; 2 (appendicitis and aggression)<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: April to May 2014. We emailed study authors twice but received no further information |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Participants were randomly assigned to methylphenidate or placebo by the following 4 strata: age (6 to 8 years; 9 to 11 years; 12 to 16 years), sex, severity of the problem according to the teachers' evaluation (Fremdbeurteilungsbogen für Hyper kinetische Störungen; sum-score > 40 and < 40) and study centre attended. Central randomisation was performed |
| Allocation concealment (selection bias) | Low risk | Central randomisation |
| Blinding of participants and personnel (performance bias) | Low risk | Study drug (or placebo) was dispensed in packages containing a weekly supply that was blinded from medical personnel and parents |
| Blinding of outcome assessment (detection bias) | Low risk | Study drug (or placebo) was dispensed in packages containing a weekly supply that was blinded from medical personnel and parents |
| Incomplete outcome data (attrition bias) | Low risk | No incomplete outcome data<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Low risk | No |
| Vested interest bias | High risk | Financial support for this study was provided by Medice Arzneimittel Pütter GmbH & Co. KG, Kuhloweg 37, D-58638 Iserlohn<br>Conflicts of interest: Dr. Doepfner is a consultant for Lilly, Medice, Novartis and Union Chimique Belge; serves on the Advisory Boards of Lilly, Medice, Shire, Novartis and Union Chimique Belge; participates as a member of the Speakers' Bureaus of Lilly, Medice, Janssen-Cilag and Union Chimique Belge; and has research contracts with Lilly, Medice, Novartis, Union Chimique Belge, the German Research Foundation and the Federal Ministry of Health. Dr. Lehmkuhl is on the Advisory Boards of Lilly and Medice. Dr. Sinzig has no financial relationships to disclose |

*Lijffijt 2006*

| Methods | Three-week, randomised, double-blind, cross-over, within-participant study conducted to test methylphenidate/placebo to assess correlations between measures of attention and inhibition with dopamine and norepinephrine blood levels<br>1. Methylphenidate<br>2. Placebo |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 15 (13 boys, 2 girls). Participants were randomly assigned to 1 of 2 possible drug condition orders<br>Number of participants followed up: 15<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-IV (combined (11%), hyperactive-impulsive (2%), inattentive (2%))<br>Age: mean 10.74 years (range 7 to 13)<br>IQ: mean 97.60<br>Methylphenidate naive: 0%<br>Ethnicity: not stated<br>Country: the Netherlands<br>Setting: out-patient clinic<br>Comorbidity: anxiety (n = 6), oppositional defiant disorder (n = 5)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. ADHD diagnosis according to DSM-IV<br>2. Participants familiar with intake of methylphenidate for at least a year<br>**Exclusion criteria**<br>1. None stated |
| Interventions | Participants were randomly assigned to different possible drug condition orders of 0.5 mg/kg or 1.0 mg/kg methylphenidate and placebo<br>Mean methylphenidate dosage: 22.67 mg<br>Administration schedule: not stated<br>Duration of each medication condition: 1 day<br>Washout before study initiation: 24 hours before testing<br>Medication-free period between interventions: no<br>Titration period: none/duration<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. Conners' Parent Rating Scale<br>2. Conners' Teacher Rating Scale<br>**General behaviour**<br>1. Child Behaviour Checklist; Teachers' Report Form<br>**Non-serious adverse events**<br>1. Paper mentioned only this: "Although side effects were minimal (a feeling of sleepiness), four participants were too fatigued after placebo or the 1.0 mg/kg dose to continue with the change task after they first completed the stop task" |

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| **Notes** | Sample calculation: no<br>Ethics approval: yes; "The study was approved by the national medical ethical committee (CCMO)"<br>**Key conclusion of study authors**<br>1. In children with ADHD, methylphenidate could act primarily on inhibitory control and is not influenced by task difficulty<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: "four participants were too fatigued after placebo or the 1.0 mg/kg dose to continue with the change task after they first completed the stop task"<br>Email correspondence with study authors: March 2014: We sent an email to the study author to request additional information but have received no reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomised |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Unclear risk | Double-blind |
| Blinding of outcome assessment (detection bias) | Unclear risk | Double-blind |
| Incomplete outcome data (attrition bias) | Low risk | No drop-outs. "All participants were familiar with the intake of MPH for at least 1 year"<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Unclear risk | No protocol available |
| Vested interest bias | Unclear risk | Not stated<br>Conflicts of interest: none declared |

*Lin 2014*

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| **Methods** | Eight-week, multi-centre (31 sites in 5 countries), double-blind, placebo-controlled, comparator (MPH-OROS), parallel study with 3 interventions<br>1. Edivoxetine<br>2. OROS methylphenidate<br>3. Placebo<br>**Phases**<br>1. Screening<br>2. Clinical treatment<br>3. Discontinuation |

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| Participants | Number of participants screened: 448<br>Number of participants included: 340 (70.6% boys, 29.4% girls). Participants were randomly assigned to 1 of 5 possible drug condition orders<br>Number of participants followed up: 210<br>Number of withdrawals: 60<br>Diagnosis of ADHD: DSM-IV-TR (combined (70.9%), hyperactive-impulsive (4.1%), inattentive (25%))<br>Age: mean 11.6 years (range 6 to 17)<br>IQ: not stated<br>Methylphenidate naive: All participants treated with methylphenidate were medication-naive. 44% of placebo-treated participants, 47% of edivoxetine-treated participants in the 0.1 mg/kg/d arm and 49% of edivoxetine-treated participants in each of the 0.2 mg/kg/d and 0.3 mg/kg/d arms had used stimulants previously<br>Ethnicity: Caucasian (72.6%), African American (not stated), Asian (not stated), Hispanic (not stated), other (not stated)<br>Country: USA, Canada, Taiwan, Mexico and Puerto Rico<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder ("less than 20%")<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. ADHD DSM-IV-TR diagnosis<br>2. > 6 years and < 17 years and 9 months of age at the time of informed consent<br>3. Diagnosis confirmed with the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Versions, and ADHD Rating Scale, Fourth Edition, score > 1.5 SD above age/sex norms and Clinical Global Impressions - ADHD - Severity Scale score > 4<br>**Exclusion criteria**<br>1. Body weight < 18 kg or > 75 kg<br>2. History of bipolar I or II disorder, or psychosis, seizure disorder or pervasive developmental disorder; motor tics or a diagnosis of Tourette's syndrome; marked anxiety, tension or agitation sufficient to contraindicate treatment with OROS methylphenidate<br>3. History of electroencephalographic abnormalities<br>4. Clinically significant abnormal ECG<br>5. Serious or unstable medical illness<br>6. Any medical condition that would markedly increase sympathetic nervous system activity (e.g. catecholamine-secreting neural tumour)<br>7. Requiring daily use of medications with sympathomimetic activity (e.g. albuterol, pseudoephedrine)<br>8. Any medical condition that would be exacerbated by an increase in norepinephrine tone<br>9. Current or past history of clinically significant hypertension |
| Interventions | Participants were randomly assigned to 1 of 4 possible drug condition orders of 18 mg, 36 mg or 54 mg OROS methylphenidate and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: 1 a day<br>Duration of each medication condition: 8 weeks<br>Washout before study initiation: all methylphenidate naive<br>Medication-free period between interventions: no<br>Titration period: none, initiated after randomisation<br>Treatment compliance: not stated |

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| **Outcomes** | **ADHD symptoms**<br>1. ADHD Rating Scale, Fourth Edition, parent-rated, Investigator-administered and -scored: weekly, parent-rated (administered and scored by qualified personnel at the investigative site based on an interview with the parent and the participant)<br>2. Clinical Global Impressions - ADHD - Improvement Scale<br>3. Clinical Global Impressions - ADHD - Severity Scale<br>4. Swanson, Nolan and Pelham Scale, Fourth Edition<br>5. Conners' Comprehensive Behavior Rating Scales<br>**Non-serious adverse events**<br>1. Adverse events, vital signs, clinical laboratory tests (e.g. chemistry, haematology, urinalysis), physical examination and ECGs<br>2. Columbia Suicide Severity Rating Scale: occurrence, severity and frequency of suicide-related thoughts and behaviours |
| **Notes** | Sample calculation: not stated<br>Ethics approval: yes<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: yes (3 participants)<br>Email correspondence with study authors: April 2015. We emailed study authors to ask for supplemental information/data but have received no response |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Interactive voice response system was used for randomisation and to determine which study drug should be dispensed |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Unclear risk | Not stated |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not stated |
| Incomplete outcome data (attrition bias) | High risk | Exclusion of methylphenidate non-responders (after randomisation) |
| Selective reporting (reporting bias) | High risk | Yes |
| Vested interest bias | High risk | Study sponsored by Ely Lilly<br>Conflicts of interest: Five authors work for Lilly |

### *Lopez 2003*

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| **Methods** | Cross-over trial with 3 interventions<br>1. Methylphenidate (Ritalin)<br>2. Concerta<br>3. Placebo<br>Phases: 4<br>1. Placebo<br>2. Concerta 18 mg<br>3. Concerta 38 mg<br>4. Methylphenidate (Ritalin LA) 20 mg<br>Evaluated on day 0, randomly assigned to drug condition on days 7, 14, 21 and 28. One practice visit for a study duration of 5 weeks in total |

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| Participants | Number of participants screened: not stated<br>Number of participants included: 36 (29 boys, 7 girls). Participants were randomly assigned to 1 of 24 (4 × 3 × 2 × 1) possible drug condition orders<br>Number of participants followed up: 36<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-IV (subtype not stated)<br>Age: mean 9 years (range 6 to 12)<br>IQ: not stated<br>Methylphenidate-naive: no<br>Ethnicity: Caucasian (36%), African American (27%), Hispanic or other (36%)<br>Country: USA<br>Setting: out-patient clinic<br>Co-morbidity: not stated<br>Co-medication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Met ADHD criteria based on Diagnostic Interview Schedule for Children<br>2. Parents consented to participation<br>**Exclusion criteria**<br>1. Concurrent significant medical or psychiatric illness or substance use disorder |
| Interventions | Participants were randomly assigned to 1 of 24 possible drug condition orders of methylphenidate (20 mg), (18 mg) Concerta, (36 mg) Concerta and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: not stated<br>Duration of each medication condition: 1 day<br>Washout before study initiation: not stated<br>Medication-free period between interventions: On the morning following each study period, participants resumed their regularly prescribed medication up to Thursday evening before the next study period day on Saturday<br>Titration period: All participants had been stabilised on an equivalent dose of 10 mg twice daily of methylphenidate before study entry<br>Treatment compliance: No participants discontinued the study prematurely |
| Outcomes | **ADHD symptoms**<br>1. Swanson, Kotkit, Agler, M-Flynn and Pelham Scale: observer, during each study period<br>**Non-serious adverse events**<br>1. Physical exam, vital signs, haematology, blood chemistries, urinalysis - screening<br>2. Adverse events: self reported, each study period<br>3. Vital signs: observer, measured every 2 hours at each study period<br>4. Adverse effects did occur in < 3% of participants exposed to each agent and dose, and 1 participant from each treatment group experienced a single mild adverse event that included abdominal pain, nausea and dyspnoea |

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| **Notes** | Sample calculation: yes<br>Ethics approval: yes<br>**Comment from study authors**<br>1. Although single blinding of raters added to the objectivity of the observations, lack of medication blinding had both negative and positive implications. On the negative side, participants may have noticed the difference in the appearance of agents administered to them, thus producing bias …[...]... another issue to contemplate is that all participants in the study had previously been stabilised on methylphenidate and, irrespective of blinding, may well have been able to identify when they were receiving placebo<br>**Key conclusion of study authors**<br>1. Although both methylphenidate (Ritalin LA) and Concerta were shown to be effective, the different release profile for each formulation can result in distinct differences between effects on measures of attention and deportment<br>**Comment from review authors**<br>1. Not able to use reported data<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: April 2014. We received supplemental information from study authors |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Order of medication assignment was determined by random assignment by a computer programme |
| Allocation concealment (selection bias) | Unclear risk | Participants were randomly assigned to 4 treatment periods. For purposes of this study, with the exception of the medicating nurse, all study personnel were blinded to the medication administered to the child |
| Blinding of participants and personnel (performance bias) | High risk | Single-blind |
| Blinding of outcome assessment (detection bias) | Low risk | For purposes of this study, with the exception of the medicating nurse, all study personnel were blinded to the medication administered to the child |
| Incomplete outcome data (attrition bias) | Low risk | None reported. No participants discontinued the study prematurely<br>Selection bias: no, but all patients were stabilised previously on methylphenidate |
| Selective reporting (reporting bias) | Unclear risk | Protocol not identified |
| Vested interest bias | High risk | The study was funded by Novartis<br>Conflicts of interest: Dr. Silva is a consultant and a member of the Speakers' Bureau for Novartis. Dr. Lopez is a consultant for Eli Lilly, Novartis and Shire. He is also a member of the Speakers' Bureaus for Novartis and Shire |

*Lufi 1997*

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| **Methods** | Cross-over trial with 2 interventions<br>1. Methylphenidate<br>2. Placebo<br>Phases: Participants randomly assigned to 3 weeks of methylphenidate, 3 weeks of placebo. No washout. Assessment at baseline and by the end of each phase |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 20 (18 boys, 2 girls). Participants were randomly assigned to 1 of 2 possible drug condition orders<br>Number of participants followed up: 20<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-IV (subtype not stated)<br>Age: mean 9.23 years (± 1.62, range 7.17 to 12.42)<br>IQ: > 70<br>Methylphenidate naive: 100%<br>Ethnicity: not stated<br>Country: Israel<br>Setting: out-patient clinic<br>Comorbidity: none<br>Comedication: no<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. IQ > 70<br>2. Treatment-naive<br>**Exclusion criteria**<br>1. Implicitly stated: gross physical impairment, intellectual deficits, major disease or serious psychological problems, and not receiving any psychological treatment prior to taking part in the research |
| **Interventions** | Participants were randomly assigned to 1 of 2 possible drug condition orders of 10 mg methylphenidate and placebo<br>Mean methylphenidate dosage: 10 mg/d<br>Administration schedule: mornings<br>Duration of each medication condition: 3 weeks<br>Washout before study initiation: All participants were treatment-naive<br>Medication-free period between interventions: none<br>Titration period: none<br>Treatment compliance: not stated |
| **Outcomes** | **ADHD symptoms**<br>1. Conners' Teacher Rating Scale<br>**General behaviour**<br>1. Global Teacher Ratings: rating scale from 1 to 10 constructed specifically for this study (assessment before ingestion of medication, after 3 weeks of first medication period, after 3 weeks of second medication period) |

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| **Notes** | Sample calculation: not stated<br>Ethics approval: not stated<br>**Comment from study authors**<br>1. Strong placebo effect<br>**Key conclusions of study authors**<br>1. Methylphenidate improved classroom behaviour as compared with no treatment<br>2. Placebo influence had almost the same effect as medication<br>3. Neither of these treatments significantly improved cognitive functioning and personality characteristics of the child with ADHD<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: September 2013. We obtained supplemental information/data from study authors |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomised |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | "everyone involved in the assessment phase ...was blind to the type of medication..."<br>All medications (both placebo and methylphenidate) were given in identical capsules to prevent recognition of the true medication |
| Blinding of outcome assessment (detection bias) | Low risk | "...the parents, the teacher, the child and the psychologist who tested the child did not know what kind of medication the child was taking..." |
| Incomplete outcome data (attrition bias) | Unclear risk | No information |
| Selective reporting (reporting bias) | Unclear risk | No information |
| Vested interest bias | Unclear risk | No information |

*Lufi 2007*

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| **Methods** | Six-week, randomised, double-blind, placebo-controlled, cross-over study conducted to detect the effects of methylphenidate on co-ordination and handwriting<br>1. Methylphenidate<br>2. Placebo |

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| Participants | Number of participants screened: 19<br>Number of participants included: 19 (12 boys, 7 girls). Participants were randomly assigned to 1 of 2 possible drug condition orders<br>Number of participants followed up: 19<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-IV (subtype not stated)<br>Age: mean 9.51 years (range 7.08 to 13.83)<br>IQ: > 70<br>Methylphenidate naive: 0%<br>Ethnicity: not stated<br>Country: Israel<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: no<br>Sociodemographics: "Participants were from a medium level social-economic status"<br>**Inclusion criteria**<br>1. Not stated<br>**Exclusion criteria**<br>1. Not stated |
| Interventions | Participants were randomly assigned to 1 of 2 possible drug condition orders of methylphenidate and placebo<br>Mean methylphenidate dosage: 0.4 mg/kg<br>Administration schedule: not stated<br>Duration of each medication condition: 3 weeks<br>Washout before study initiation: no<br>Medication-free period between interventions: yes<br>Titration period: not stated<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. Conners' Abbreviated Symptom Questionnaire (teacher): assessed at baseline, weeks 3 and 6<br>**General behaviour**<br>1. Achenbach's Teacher Report: assessed at baseline, weeks 3 and 6 |

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| **Notes** | Sample calculation: not stated<br>Ethics approval: not stated<br>**Comments from study authors (limitations)**<br>1. Limited group of participants<br>2. Use of only 1 dosage level<br>**Key conclusions of study authors**<br>1. Results show that methylphenidate improved some cognitive functions of eye-hand co-ordination slightly better than placebo<br>2. Behaviour variables assessed by teachers improved only under the influence of methylphenidate<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: no drop-outs<br>Email correspondence with study authors: October 2013. We obtained additional information on IQ from the first study author |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "Randomized" |
| Allocation concealment (selection bias) | Unclear risk | "The study was designed as a double-blind, randomized, crossover, placebo-control procedure" |
| Blinding of participants and personnel (performance bias) | Low risk | "Each participant was given exactly 0.4 mg/kg of MPH in special capsules of MPH and a placebo to avoid recognition of the medication" |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not stated |
| Incomplete outcome data (attrition bias) | Low risk | No drop-outs<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Unclear risk | No protocol available |
| Vested interest bias | Unclear risk | Not stated<br>Conflicts of interest: not stated |

*Manos 1999*

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| **Methods** | Four-week, double-blind titration, placebo-controlled protocol. Cross-over trial with 2 interventions in 4 doses<br>1. Methylphenidate 5 mg × 2 daily<br>2. Methylphenidate 10 mg × 2 daily<br>3. Methylphenidate 15 mg × 2 daily<br>4. Placebo × 2 daily<br>**Phases**<br>1. Cross-over trial with Adderall and methylphenidate. First phase was not blinded. (The child's paediatrician or family physician determined whether methylphenidate or Adderall should be prescribed; criteria were the physician's familiarity with the agent and whether he or she wanted the participant to receive a single dose (Adderall) or a twice-daily dose (methylphenidate) of medication treatment for ADHD.) Second phase: A 1-of-3 medication dose sequence was randomly assigned. 15 mg methylphenidate was always given after 10 mg methylphenidate<br>2. 42 of the 117 participants receiving methylphenidate were matched, with 42 receiving Adderall<br>3. Best dose was compared with placebo. Best dose was assigned by consensus of a clinical child psychologist and a board-certified child and adolescent psychiatrist before the medication blind was broken<br>Manos 1999: Seven youths given methylphenidate and 4 given Adderall did not receive the 15 mg dose of medication. The decision to forego the 15 mg condition was based on the paediatrician's assessment that the child was too young or underweight for this high dose and our assessment that the best dose had already been achieved at a lower dose |
| **Participants** | Number of participants screened: 195<br>Number of participants included: 177. Participants were randomly assigned to different possible drug condition orders<br>Number of participants followed up: 134<br>Number of withdrawals: 43<br>Diagnosis of ADHD: DSM-IV (combined (55%), inattentive (45%))<br>Age: mean 10.1 years (SD not stated, range 5 to 17)<br>IQ: > 70<br>Sex: 33 boys, 9 girls<br>Methylphenidate naive: not stated<br>Ethnicity: Caucasian (93%), African American (7%), Asian (0%), Hispanic (0%), others (0%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: no significant comorbid disorders. Although no formal comorbidity data are available, it appears that psychiatric comorbidity was modest in this cohort<br>Comedication: not stated<br>Sociodemographics: predominantly well educated<br>Manos 1999 and Faraone 2002: 42 were participants matched to the Adderall group in order of diagnostic category, age and sex. Only these 42 of 117 receiving methylphenidate were compared with the Adderall group<br>Findling 2001a: 195 youths entered the study. Data for a best dose were provided for 177 participants: 111 in the methylphenidate group, 66 in the mixed amphetamine salts group<br>Diagnosis of ADHD: inattentive (47%), combined (53%). Inattentive subtype is overrepresented in the older age group<br>Age group: 4 to 8 years (mean 6.35) 69 (57 boys); 8 to 11 years (mean 9.47) 56 (45 boys); 11 to 17.59 years (mean 13.64) 52 (41 boys)<br>Sociodemographics: No significant differences in baseline demographics were noted between groups<br>**Findling 2001b** |

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| | Number of participants included: 195<br>Number of participants completed: 137: methylphenidate 82, Adderall 55<br>Diagnosis of ADHD: DSM-IV (combined (57%), inattentive (43%))<br>Age: mean 10 years (SD not stated, range 4 to 17)<br>IQ: > 70<br>Sex: 66 boys, 16 girls<br>Ethnicity: Caucasian (84%), African American (6%), other (10%)<br>Country: USA<br>Comorbidity: without significant comorbid disorders<br>Comedication: possible, but not recorded<br>Sociodemographics: predominantly well educated. No differences in sex, ethnicity or ADHD subtype were found between methylphenidate and Adderall groups. No participants had a history of hypertension, hypotension or clinically significant cardiovascular disease<br>**Inclusion criteria**<br>1. All children diagnosed with ADHD met full DSM-IV diagnostic criteria for this disorder. Criteria include (1) presence of ≥ 6 symptoms for inattention and/or ≥ 6 symptoms for hyperactivity/impulsivity; (2) symptoms significantly interfering with functioning at home and at school as noted during structured or semi structured clinical interviews with the Computerized Diagnostic Interview for Children; (3) symptom severity on broad-band (i.e. Conners' Abbreviated Symptoms Questionnaire (Conners, 1969)) and narrow-band (e.g. ADHD Rating Scale (DuPaul, 1991)) rating scales at threshold or above (i.e. rated 2 or 3); (4) multiple raters (e.g. parents, teachers) who agreed to the presence of the symptoms; and (5) empirical comparison with norms indicating ≥ 1/5 SD cutoff on ≥ 1 rating scale. It should be noted that in identifying the presence of symptoms, behaviours across informants were not pooled observations. Behaviours were considered significant only if 2 informants agreed to the presence of the symptom on rating scales or in interviews<br>**Exclusion criteria**<br>1. No patients were excluded from the trial per se |
| Interventions | Participants were randomly assigned to different orders of 5 mg, 10 mg or 15 mg methylphenidate and placebo<br>Mean methylphenidate dosage: best dose 9.1 mg to 10.4 mg<br>Administration schedule: morning (at 8.00 AM) and noon<br>Duration of each medication condition: 1 week<br>Washout before study initiation: none<br>Titration period: none<br>Treatment compliance: 11 terminated because of adverse events |

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| **Outcomes** | ADHD symptoms<br><br>**Findling 2001:** compared treatment for children and adolescents and weight-adjusted dosing of methylphenidate. Measurement instruments include the following<br><br>1. ADHD Rating Scale<br>2. Abbreviated Symptoms Questionnaire (Conners)<br>3. Composite Rating and School Situations Questionnaire Revised, parent and teacher. Composite Rating, also observer-rated. Rating every seventh day of each week's dose and baseline. Best dose evaluated and compared with placebo and Adderall<br><br>Best dose based only on Abbreviated Symptoms Questionnaire - Teacher. Does not separate methylphenidate and mixed amphetamine salts in tables<br><br>**Non-serious adverse events**<br><br>1. Side Effects Behavior Monitoring Scale by parents every week (symptoms were considered problematic if parents rated them as ≥ 5)<br>2. Blood pressure and pulse every week<br><br>**Findling 2001b**<br><br>1. Blood pressure and pulse |
| **Notes** | Sample calculation: Not stated<br><br>Ethics approval: Not stated<br><br>**Key conclusions of study authors**<br><br>1. Manos 1999: Both methylphenidate and Adderall have been shown to be effective treatments for children with ADHD<br>2. Farone 2002: The present report extends this prior work by applying drug–placebo response curve methods to the data reported by Manos et al. (1999). Results show that the efficacy of Adderall and methylphenidate in improving functioning is seen throughout the full range of improvement scores. Both drugs prevent worsening and, for most patients, lead to improvements that are well into the normal range<br>3. Findling 2001a: Data suggest that psychostimulants are equally effective in treating children and adolescents with ADHD. Adolescents with ADHD may not necessarily require more medication than younger children to achieve a similar therapeutic response<br>4. Findling 2001b: Short-term cardiovascular effects of both Adderall and methylphenidate were modest. No participants experienced any clinically significant change in these cardiovascular measures during the course of this brief trial<br><br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; 15 youths in the Adderall sample had been tried on methylphenidate before enrolment in this medication trial. Because of lack of response or serious side effects, these children discontinued use of methylphenidate. A total of 37% of the Adderall sample subsequently was composed of children who had unsuccessfully used methylphenidate but successfully responded to Adderall<br><br>Any withdrawals due to adverse events: yes; Findling 2001a (11/195), due to multiple adverse events<br><br>Email correspondence with study authors: April 2014. Emailed study authors twice to request additional data but have received no answer |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | High risk | First phase not blinded. Methylphenidate is a selected group |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | High risk | Clinician, teacher and parent were blinded only to dose, not to medication |
| Blinding of outcome assessment (detection bias) | High risk | Clinician, teacher and parent were blinded only to dose, not to medication |
| Incomplete outcome data (attrition bias) | Unclear risk | Only best dose compared with placebo. Findling (Abbreviated Symptoms Questionnaire) + 30 participants. Of 43 participants with < 4 weeks of data, 30 had only 3 weeks of data because physicians considered them too young or too small to receive 15 mg before initiating protocol |
| Selective reporting (reporting bias) | Unclear risk | No protocol identified |
| Vested interest bias | High risk | Study was supported in part by funding from Shire Pharmaceutical Development Incorporated to Dr. Faraone<br>Conflicts of interest: Study authors acknowledge partial support to the second author from the National Institute on Drug Abuse (NIDA) (grants R01-DA07957 and MCJ-390592) and from the Maternal and Child Health Program, Health Resources and Service Administration, Department of Health and Human Services (grant 390715), and to the third author from the Stanley Foundation |

*Martins 2004*

| Methods | Four-week-long, double-blind, randomised, parallel trial with 2 interventions<br>1. Methylphenidate group: methylphenidate, 7 days a week<br>2. Placebo group: methylphenidate Monday through Friday, and placebo on weekends |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 40 (all boys)<br>Number of participants randomly assigned: methylphenidate 21, placebo 19<br>Number of participants followed up: methylphenidate 19, placebo 19<br>Number of withdrawals: methylphenidate 2, placebo 0<br>Diagnosis of ADHD: DSM-IV (combined (92.5%))<br>Age: mean methylphenidate 9 years (SD 2.2, range 6 to 14), placebo 9.6 years (SD 2.8, range 6 to 14)<br>IQ: mean, methylphenidate 97.3, placebo 93.5<br>Methylphenidate naive: not stated<br>Ethnicity: European-Brazilian: methylphenidate 16 (76.2%), placebo 15 (78.9%)<br>Country: Brazil<br>Setting: out-patient clinic<br>Comorbidity: yes; conduct or oppositional defiant disorder (methylphenidate 57.2%, placebo 57.9%)<br>Comedication: not stated, no psychiatric medication<br>Sociodemographics: Monthly family income was calculated according to the following formula: total monthly income received by all members of the family (expressed in number of minimum wages) divided by the number of persons in the family. A value lower than 0.7 (approximately US$ = 68 per family member per month) is usually an indicator of poverty in Brazil. Methylphenidate 3.3, placebo 2.4. No significant differences in baseline demographics were noted between the 2 groups<br>**Inclusion criteria**<br>1. ADHD diagnosis according to DSM-IV criteria<br>2. Between 6 and 14 years of age<br>3. Male<br>4. Education level between first and eighth elementary grades<br>**Exclusion criteria**<br>1. Presence of significant neurological or clinical disease<br>2. Presence of bipolar disorder or substance abuse/dependence disorder<br>3. Use of any psychiatric medication in the past 6 months, including methylphenidate<br>4. Estimated IQ < 70 |
| Interventions | Participants were randomly assigned to methylphenidate 7 days a week or to methylphenidate on weekdays and placebo on weekends<br>Mean methylphenidate dosage: Initial dose of methylphenidate was 0.3 mg/kg/d the first week. Dose was raised to 0.5 mg/kg/d the second week and to 0.70 mg/kg/d the third and fourth weeks<br>Administration schedule: twice a day: breakfast and lunch<br>Duration of intervention: 4 weeks<br>Titration period: none<br>Treatment compliance: Only 7 of 160 blister packs were returned with unused pills |
| Outcomes | **ADHD symptoms**<br>1. 10-item Conners' Abbreviated Rating Scale (Conners 1985). Rated every Monday after school by both teachers and parents<br>**Serious adverse events**<br>1. Barkley Side Effect Rating Scale<br>a. Number of adverse effects reported<br>b. Mean severity of reported adverse effects<br>(Completed only by parents for assessment of side effects on weekends) |

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| **Notes** | Sample calculation: no<br>Ethics approval: approved by the Ethical Committee of the Hospital de Clínicas de Porto Alegre (HCPA) (approved as an International Review Board (IRB) by the Office for Human Research Protections, United States of America)<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: no<br>**Comments from study authors**<br>1. Context established by the home setting on the weekend may have created conditions in which the effects of methylphenidate were minimal or insignificant, because children may have been involved in play activities much of the time<br>2. It is reasonable to suggest that during the weekend, when networks related to ADHD neurobiology might be demanded less often, differences between drug and placebo would be more difficult to detect<br>3. It is possible that parental tolerance of ADHD symptoms on weekends might be greater than on weekdays. Our findings may not be generalisable to females<br>**Key conclusion of study authors**<br>1. Our findings suggest that weekend holidays during methylphenidate administration reduce the side effects of insomnia and appetite suppression without causing a significant increase in ADHD symptoms, on weekends or on the first day of school after the weekend (Monday)<br>Email correspondence with study authors: We have contacted study authors several times to ask for additional information about data, but we have received no data from this study that we can use |

## Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomised, double-blind, parallel-group design was used. Participants were randomly assigned to 1 of 2 groups, according to a computer-derived algorithm (EPIINFO.06) |
| Allocation concealment (selection bias) | Low risk | Computer-derived algorithm |
| Blinding of participants and personnel (performance bias) | Low risk | Methylphenidate and placebo pills were of the same shape and colour |
| Blinding of outcome assessment (detection bias) | Unclear risk | Double-blind. No other information |
| Incomplete outcome data (attrition bias) | Low risk | Measured adherence to protocol by assessing returned, unopened blister packs. None of the findings in the analyses was significantly affected by the 2 participants (they did not follow the protocol as stated by researchers) from the methylphenidate group who did not receive a few doses appropriately on weekends or on Monday. Some teacher ratings (8.5%) were missed because of the child's absence from school on a specific day of evaluation or because of a school holiday<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Low risk | No reporting bias |
| Vested interest bias | Unclear risk | Methylphenidate and placebo pills were supplied by Novartis Pharmaceuticals (São Paulo, Brazil) at no cost and without restrictions. No additional funding was requested or received from Novartis or any other commercial entity<br>Conflicts of interest: Study authors have reported no conflicts of interest |

*McBride 1988a*

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| **Methods** | Individual, double-blind, cross-over trial for 4 weeks with 2 interventions<br>1. Methylphenidate<br>2. Placebo |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 73. Participants were randomly assigned to 1 of 2 possible drug condition orders<br>Number of participants followed up: 70 (53 boys, 17 girls)<br>Number of withdrawals: 3<br>Diagnosis of ADHD: DSM-III (77% met the criteria for ADD with hyperactivity)<br>Mean age: methylphenidate responders 8.5 (SD not stated), methylphenidate non-responders 9.5 (SD not stated). Range 6 to 17 years<br>Mean IQ: methylphenidate responders 102 (SD 21), methylphenidate non-responders 89 (SD 23)<br>Methylphenidate naive: 71 (97%)<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: carbamazepine or phenytoin or valproic acid or mephobarbital (6.4 receiving a combination of these drugs). Clonidine (n = 1)<br>Sociodemographics: no information<br>**Inclusion criteria**<br>1. Referred because the child's academic performance was below that expected on the basis of his abilities, as documented by psychological testing, or because his behavioural dysfunction was interfering with self-image and socialisation, or for both reasons<br>2. 6 to 17 years of age<br>3. No child was excluded from the trial on the basis of low intelligence, history of seizures or concurrent medication<br>**Exclusion criteria**<br>1. Not stated |
| **Interventions** | Participants were randomly assigned to 1 of 2 possible drug condition orders of 0.3 mg/kg methylphenidate and placebo. Methylphenidate was rounded to the nearest 1.25 mg<br>Mean methylphenidate dosage: no information, but mean dose during follow-up was 0.36 mg/kg/dose<br>Administration schedule: morning and 4 hours later<br>Duration of each medication condition: 2 weeks<br>Washout before study initiation: none<br>Medication-free period between interventions: none<br>Titration period: none<br>Treatment compliance: no information |

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| Outcomes | **ADHD symptoms**<br>1. Abbreviated Conners' Teacher and Parent Questionnaire<br>2. Parent Questionnaires was rated at the end of each weekend and at the end of each school week. Teacher Questionnaires were filled out at the end of the week<br>**Serious adverse events**<br>1. No serious side effects during the trial<br>**Non-serious adverse events**<br>1. No information about how data on side effects were obtained<br>None of the parents of responders who had experienced side effects during the trial thought the effects were significant enough that they should not treat their child with methylphenidate, and no side effects other than appetite suppression continued during regular therapy after the trial<br>Follow-up 6 months after: n = 33. 15 had no change in weight curves. 1 gained 7 kg beyond his original percentile |
| Notes | Sample calculation: no information<br>Ethics approval: no information<br>**Comments from study authors**<br>1. Participants in this study were not a randomly selected group of children with ADD but, rather, a referral population already screened by their school psychologists and primary care physicians<br>2. Individual children with differing absorption, metabolism or underlying neurochemical abnormality may have different response thresholds, and potential responders may have been overlooked because they did not consistently try a higher dose<br>3. 15% of children with ADD in this study were adopted<br>4. The finding that non-responders were older may reflect the development of secondary characteristics such as decreased motivation and poor study habits in long-term ADD -symptoms not easily reversed during a short trial<br>5. A problem inherent in this trial, as in an open trial, is dependence on the observations of teachers and parents who have variable observational skills, variable tolerance for symptoms of ADD and different perspectives on medication<br>6. Lower Conners' scores may be explained by the fact that many characteristics rated on Conners' questionnaires reflect hyperactivity, and some of these children were more inattentive than hyperactive<br>**Key conclusions of study authors**<br>1. 51 (of 70) children showed improvement during 1 of the 2-week periods, and that period corresponded with methylphenidate therapy in 48<br>2. 6 of the 22 who did not respond to methylphenidate experienced worsening of function while taking the drug. No serious side effects were reported during the trial<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | High risk | The pharmacist labelled the 2 sets of capsules as “Medicine A” and “Medicine B” in either order by coin flip for the first 22 trials, and then by using a random numbers table |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | The manner of labelling was sealed by the pharmacist in an envelope that was not opened until the trial had ended and findings had been discussed with the parents |
| Blinding of outcome assessment (detection bias) | Unclear risk | Objectivity was lessened for a few parents because the decreased appetite associated with methylphenidate led them to suspect which capsules contained the drug |
| Incomplete outcome data (attrition bias) | Low risk | In the few trials for which 1 to 3 of 10 items on Conners' questionnaire had not been scores, the score was prorated based on 30 points maximum<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Low risk | None |
| Vested interest bias | Unclear risk | No information |

*McGough 2006*

| Methods | Phase II, randomised, double-blind, placebo-controlled, laboratory-classroom, cross-over study with a lead-in open-label dose-optimisation phase<br>1. Mehtylphenidate transdermal system<br>2. Placebo |
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| Participants | Number of participants screened: 93<br>Number of participants included: 80<br>Number of participants randomly assigned: methylphenidate 80, placebo 80 (cross-over)<br>Number of withdrawals: 7 "adverse events", 3 consent withdrawn, 2 lost to follow-up, 1 because of "lack of efficacy". 1 participant discontinued because of "protocol violation"<br>Diagnosis of ADHD: DSM-IV-R (combined 62 (79%), hyperactive-impulsive 4 (5%), inattentive 13 (17%))<br>Age: mean 9.1 years (SD 1.7, range 6 to 12)<br>IQ: > 70<br>Sex of baseline participants included in ITT: 57 boys (72%), 22 girls (28%)<br>Methylphenidate naive: 37%<br>Ethnicity: Caucasian 55 (70%), African American 8 (10%), Asian 2 (3%), other 14 (18%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: no<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. 6 to 12 years of age inclusive<br>2. ADHD DSM-IV diagnosis using Kiddie Schedule for Affective Disorders and Schizophrenia and psychiatric assessment<br>3. ADHD Rating Scale score ≥ 26 at baseline/unmedicated<br>4. Normal laboratory parameters and vital signs including ECG<br>**Exclusion criteria**<br>1. Comorbid psychiatric diagnosis (apart from oppositional defiant disorder)<br>2. History of seizures<br>3. History of tic disorders<br>4. Mental retardation<br>5. Any illness or skin disorder that might jeopardise safety or compromise study assessments<br>6. No clonidine, atomoxetine, antidepressants, investigational medications, hepatic P450 enzyme-altering agents, medications with central nervous system effects, sedatives, anxiolytics or antipsychotics within the 30 days before screening |
| Interventions | Participants were randomly assigned to 1 of 2 possible drug condition orders of methylphenidate and placebo<br>Mean methylphenidate dosage: "At the end of the dose optimization phase of the study, the majority of patients (78%) were optimized to either the 16 mg or 20 mg dosage strengths"<br>Administration schedule: once daily<br>Duration of each medication condition: 1 week<br>Washout before study initiation: "up to 28 days"<br>Medication-free period between interventions: 4:00 PM to 7:00 AM the next day (15 hours)<br>Titration period: 5-week dose-optimisation phase<br>Treatment compliance: "During the laboratory classroom period, 97% and 96% of participants were compliant with [methylphenidate transdermal system] MTS and placebo treatments respectively" |

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| Outcomes | **ADHD symptoms**<br>1. Primary outcome<br>a. Swanson, Kotkit, Agler, M-Flynn and Pelham Scale at multiple time points: pre-dose and 2, 3, 4, 5, 6, 7.5, 9. 10.5 and 12 hours post dose<br>b. ADHD Rating Scale, Fourth Edition (administered at each visit)<br>c. Conners' Parent Rating Scale - Revised Short Version (Conners 1997a). Completed at 11:00 AM and 3:00 PM on the Sunday before the first visit and subsequently, before each visit to the centre<br>"The mean values of the CPRS-R over the 11:00 AM and 3:00 PM time points were used in the analysis"<br>**General behaviour**<br>1. Clinical Global Impressions - Severity and - Improvement scales as well as the Parent Global Assessment<br>**Non-serious adverse outcomes**<br>1. Vital signs, blood pressure, pulse, oral temperature, respiratory rate, height, weight, laboratory measures, physical examination, dermal evaluation |
| Notes | Sample calculation: yes<br>Ethics approval: yes<br>**Key conclusions of study authors**<br>1. Treatment with methylphenidate transdermal system resulted in statistically significant improvement in all efficacy measures<br>2. Time course and therapeutic effects of methylphenidate transdermal system suggest that this novel methylphenidate delivery system provides efficacious once-daily treatment for ADHD<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; "Participants were either known to be responsive to stimulants or naive to stimulant treatment"<br>Any withdrawals due to adverse events: yes; 7/93 participants were withdrawn because of adverse effects during the dose-optimisation period (i.e. before randomisation)<br>Email correspondence with study authors: June 2014. We obtained supplemental information regarding risk of bias. Additional data were not available ( Ramstad 2013a [pers comm] ) |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "Participants were randomized into either 1 week of [methylphenidate transdermal system] MTS or 1 week of [placebo transdermal system] PTS (in their individually optimized dose) and were crossed over to the opposite treatment the following week"<br>From correspondence: "Participants were randomized centrally for each of the study conditions. Randomization codes were not available to site study staffs, but were provided to research pharmacies at each site which corresponded to a particular dose pack" (Ramstad 2014 [pers comm]) |
| Allocation concealment (selection bias) | Low risk | See above |
| Blinding of participants and personnel (performance bias) | Low risk | "Phase-II randomized, double-blind, placebo-controlled laboratory classroom, crossover study with a lead-in open-label dose optimization phase"<br>From correspondence: "Active and inactive patches were identical in appearance" (Ramstad 2014 [pers comm]) |
| Blinding of outcome assessment (detection bias) | Low risk | See above |
| Incomplete outcome data (attrition bias) | High risk | Safety population according to Table Two is n = 93. Table Six lists safety data for n = 80 participants only. Safety data for 13 participants appear to be "missing" - including those from participants withdrawn before randomisation as the result of adverse events |
| Selective reporting (reporting bias) | High risk | Safety population according to Table Two is n = 93. Table Six lists safety data for n = 80 participants only. Safety data for 13 participants appear to be "missing" - including those from participants withdrawn before randomisation as the result of adverse events |
| Vested interest bias | High risk | "This study was supported by funding from Shire US Inc"<br>Conflicts of interest: Two medical writers acknowledged (Amy M. Horton & Michelle Roberts) but were unclear about where they came from or what their role was in the publication |

*McInnes 2007*

| Methods | Cross-over trial with 2 interventions<br>1. Methylphenidate at low, medium and high doses<br>2. Placebo<br>Phases: 4 |
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| Participants | Number of participants screened: 17<br>Number of participants included: 16 (12 boys, 4 girls). Participants were randomly assigned to 1 of 12 possible drug condition orders<br>Number of participants followed up: 16<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-IV-TR (combined (63%), hyperactive-impulsive (6%), inattentive (31%))<br>Age: mean 9.2 years (range 7 to 12)<br>IQ: mean 107.7 (range not reported)<br>Methylphenidate naive: ~ 80%<br>Ethnicity: not stated<br>Country: Canada<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder (19%), conduct disorder (25%), generalised anxiety disorder (31%)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Children 7 to 12 years of age with ADHD referred to an out-patient neuropsychiatry clinic for evaluation of response to methylphenidate<br>**Exclusion criteria**<br>1. Children with low cognitive performance (IQ < 80) |
| Interventions | Participants were randomly assigned to 1 of 12 possible drug condition orders of low, medium and high methylphenidate and placebo<br>Mean methylphenidate dosage: low (mean 0.21 mg/kg to 0.33 mg/kg, SD 0.07 to 0.02); medium (mean 0.31 mg/kg to 0.43 mg/kg, SD 0.09 to 0.03); and high (mean 0.42 mg/kg to 0.65 mg/kg, SD 0.13 to 0.15) methylphenidate Administration schedule: 1 per day at 9:00 AM<br>Duration of each medication condition: 1 day<br>Washout before study initiation: 48 hours before study<br>Titration period: none<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. Inattention/overactivity symptoms based on 5/10 items from the Iowa Conners' Rating Scale, rated by observer 90 to 120 minutes after ingestion of capsule |

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| **Notes** | Sample calculation: no<br>Ethics approval: yes<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Comments from study authors**<br>1. With respect to the medication protocol, we cannot predict that similar results would hold with longer-term treatment with methylphenidate, given that these findings were obtained under a single acute drug challenge<br>2. Our findings for a predominantly male group of children with ADHD may not be generalisable to other groups of children with ADHD, for example, community samples that involve more girls and different rates of occurrence of comorbid conditions<br>3. Small sample size places limitations on conclusions that can be drawn from our findings<br>**Key conclusions of study authors**<br>1. Findings provide preliminary evidence that methylphenidate affects higher-level language comprehension skills, which require sustained attention and mental effort<br>2. If generalisable to classroom listening skills, these findings have implications for clinicians and teachers involved with children with ADHD |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not described |
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Blinding of participants and personnel (performance bias) | Low risk | 'Multiple blind procedures', capsules identically packaged by pharmacists |
| Blinding of outcome assessment (detection bias) | Low risk | 'Examiner, who was kept blind to child's medication status' |
| Incomplete outcome data (attrition bias) | Low risk | No LTFU<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | High risk | Symptom data not reported |
| Vested interest bias | High risk | Supported by funds from The Psychiatric Endowment Fund<br>Conflicts of interest: Study authors had received funding from Eli Lilly, Shire Pharmaceuticals, Janssen-Ortho and McNeil Pharmaceuticals |

*Moshe 2012*

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| **Methods** | Two-week, randomised, double-blind, cross-over trial with 2 interventions<br>1. Methylphenidate<br>2. Placebo |

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| Participants | Number of participants screened: 78<br>Number of participants included: 57 (all boys). Participants were randomly assigned to 1 of 2 possible drug condition orders<br>Number of participants followed up: 57<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-IV (combined and hyperactive-impulsive (53%), inattentive (47%))<br>Age: mean 9.5 years (range 7 to 12)<br>IQ: normal<br>Methylphenidate naive: 100%<br>Ethnicity: not stated<br>Country: Israel<br>Setting: out-patient clinic<br>Comorbidity: no<br>Comedication: no<br>Sociodemographics: representing all socioeconomic strata<br>**Inclusion criteria**<br>1. Male<br>2. 7 to 12 years<br>3. ADHD, DSM-IV<br>4. Drug-naive and with no other intervention<br>5. Suitable candidate for methylphenidate treatment<br>6. Attention disorder was associated with a significant effect on daily life, and scores on 1 of the Attention subscales of both parent and teacher questionnaires were 1.5 SD or above the mean as suggested in clinical guidelines<br>**Exclusion criteria**<br>1. Chronic psychiatric and neurological disorders, for example, obsessive-compulsive disorder<br>2. Tourette's syndrome<br>3. Seizure disorder<br>4. Severe learning disability (defined by special education enrolment)<br>5. Definitive primary diagnosis of an anxiety disorder (DSM-IV) or sensory impairment |
| Interventions | Participants were randomly assigned to 1 of 2 possible drug condition orders of 0.3 mg/kg immediate-release methylphenidate and placebo<br>Methylphenidate dose range: 6 mg to 12 mg<br>Administration schedule: once daily<br>Duration of each medication condition: 1 week<br>Washout before study initiation: no (drug-naive)<br>Titration period: no<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. Conners' Teacher Rating Scale, revised: weekly (after each intervention period) |

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| **Notes** | Sample calculation: yes<br>Ethics approval: yes<br>**Comments from study authors**<br>1. Results of the present study should be interpreted with caution<br>2. As only boys were included, the results might not be valid for girls<br>3. Children were clinic referrals and therefore might not be representative of the population of children with ADHD at large<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: April to October 2013. We received supplemental data from study authors |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomly assigned with a table of random numbers |
| Allocation concealment (selection bias) | Low risk | Placebo (prepared as look-alike capsules by the hospital pharmacy) |
| Blinding of participants and personnel (performance bias) | Low risk | Double-blind |
| Blinding of outcome assessment (detection bias) | Low risk | Double-blind |
| Incomplete outcome data (attrition bias) | Unclear risk | No information<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Low risk | According to study authors, all planned outcomes were assessed and analysed |
| Vested interest bias | Low risk | Not funded<br>Conflicts of interest: none declared |

*Muniz 2008*

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| **Methods** | Randomised, multi-centre, double-blind, 5-period, cross-over trial in a laboratory classroom setting with 3 interventions<br>1. Extended-release dexmethylphenidate<br>2. Extended-release racemic methylphenidate hydrochloride<br>3. Placebo<br>Phases: extended-release dexmethylphenidate 20 mg/d, extended-release dexmethylphenidate 30 mg/d, extended-release racemic methylphenidate hydrochloride 36 mg/d, extended-release racemic methylphenidate hydrochloride 54 mg/d and placebo |

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| Participants | Number of participants screened: 84<br>Number of participants included: 84 (55 boys, 29 girls). Participants were randomly assigned to 1 of 5 possible drug condition orders<br>Number of participants followed up: 81<br>Number of withdrawals: 3<br>Diagnosis of ADHD: DSM-IV (combined (89.3%), inattentive (10.7%))<br>Age: mean 9.5 years (SD 1.7, range 6 to 12)<br>IQ: not stated<br>Methylphenidate naive: 0%<br>Ethnicity: Caucasian (42.9%), African American (27.4%), Hispanic (28.6%), other (1.2%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: no<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. DSM-IV diagnosis of ADHD using Diagnostic Interview Schedule for Children<br>2. On stabilised total daily dose or nearest equivalent dose of 40 mg to 60 mg of extended-release racemic methylphenidate hydrochloride or 20 mg to 30 mg extended-release dexmethylphenidate for ≥ 2 weeks before screening visit<br>**Exclusion criteria**<br>1. Tic disorder or Tourette's syndrome<br>2. History of a seizure disorder<br>3. Psychiatric illness<br>4. Substance abuse disorder<br>5. Taking prohibited concomitant medications or ADHD medication other than methylphenidate<br>6. Taking antidepressant or psychotropic medications<br>7. Had begun psychotherapy within 3 months before randomisation<br>8. Home-schooled children<br>9. Females of child-bearing potential with positive urine pregnancy test before enrolment (or, if sexually active, not using adequate and reliable contraception) |
| Interventions | Participants were randomly assigned to 1 of 5 possible drug condition orders of extended-release dexmethylphenidate 20 mg/d, 30 mg/d, 36 mg/d, 54 mg/d and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: once daily. Morning dosing as 2 capsules Sunday to Saturday. 6 doses were administered at home (Sunday to Friday), and the Saturday dose was administered by research staff. This was repeated until all 5 treatments had been administered. Mean duration of exposure to study medication was 7 days for all 5 treatments<br>Washout before study initiation: 6 days medication-free<br>Titration period: "On stabilized total daily dose or the nearest equivalent dose of 40 to 60 mg of d,l-MPH or 20 to 30 mg d-MPH for at least 2 weeks prior to the screening visit" initiated before randomisation<br>Treatment compliance: not stated |

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| Outcomes | **ADHD symptoms**<br>1. Primary efficacy variable<br>a. Change from pre-dose Swanson, Kotkit, Agler, M-Flynn and Pelham (SKAMP) Rating Scale-Combined score at 2 hours post dose with extended-release dexmethylphenidate 20 mg/d compared with extended-release racemic methylphenidate hydrochloride 36 mg. This change was calculated by subtracting the pre-dose value (hour 0 score) from the post-dose value<br>2. Secondary outcome measures<br>a. Change from pre-dose (0 hour) on Combined, Attention and Deportment subscores of the Swanson, Kotkit, Agler, M-Flynn and Pelham Scale, at specified intervals post dose (0.5, 1, 2, 3, 4, 6, 8, 10, 11 and 12 hours), and **a**rea **u**nder the score vs time **c**urve (AUC) of the change from pre-dose in Combined score from hour 0 to hour 4 (AUC 0 to 4), and from hour 0 to hour 12 (AUC 0 to 12)<br>**General behaviour**<br>1. "The Conners' Parent Rating Scale (CPRS), a 27-item questionnaire designed to evaluate children's behaviour (Conners 1998a), was completed by parents on the Practice Day to assess behaviour without medication and at each subsequent assessment day to rate the child's behaviour during the previous week"<br>**Serious adverse events**<br>1. Safety assessments consisted of monitoring and recording of all adverse events<br>**Non-serious adverse events**<br>1. Safety assessments consisted of monitoring and recording all adverse events and recording vital signs and body weight at each visit<br>2. Laboratory parameters (including haematology, blood chemistry and urinalysis), ECGs and results of physical examinations were assessed for abnormalities at screening and final visits (no final visit assessments were carried out for ECGs and physical examinations) |
| Notes | Sample calculation: yes; "It was determined that approximately 90 patients were required to detect a 0.05-level treatment difference at 84% power assuming a difference and standard deviation of 3.5 and 11 for SKAMP-Combined score, at 2 hours post-dose using a paired t-test"<br>Ethics approval: no information<br>**Key conclusions of study authors**<br>1. "The results of this study demonstrated that all active treatments generally provided significant improvement in ADHD symptoms over placebo over 11 to 12 hours postdose in children 6–12 years old"<br>2. "The primary efficacy variable, adjusted mean change in SKAMP-Combined score from pre-dose to 2 hours post-dose, was significantly greater during treatment with d-MPH-ER 20 mg/day than d,l-MPH-ER 36 mg/day (adjusted mean change 10.65 and 5.94, respectively; p 0.001). Similar results at two hours post-dose were noted for the secondary measure of SKAMP-Combined score comparing d-MPH-ER 30 mg/day with d,l-MPH-ER 54 mg/day (adjusted mean change 11.17 and 7.52, respectively; p0.001)."<br>**Comment from review authors**<br>1. We did not include the Swanson pencil and paper math test of "academic productivity" among ADHD outcome measures. This may be seen as an ADHD outcome measure, but it does not specifically measure the 3 key ADHD core signs of inattention, hyperactivity and impulsivity<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; "Children recruited for this study had been stabilized on a total daily dose or the nearest equivalent dose of 40 to 60 mg of d,l-MPH or 20 to 30 mg d-MPH for at least 2 weeks prior to the screening visit" - so presumably non-responders to methylphenidate and those experiencing intolerable adverse events while taking methylphenidate were not included<br>Email correspondence with study authors: July 2014. Emailed study authors to ask for additional information but have not received a reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "A total of 84 subjects were randomized to receive treatment and were included in the efficacy and safety analyses" |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Low risk | "After the Practice Day, the first assigned treatment was dispensed to the parents as blinded capsules according to their child's randomized sequence. To maintain blinding, all treatments were over-encapsulated and the same number of capsules were given once daily for each sequence" |
| Blinding of outcome assessment (detection bias) | Low risk | "The ratings were based on the frequency and quality of behaviours as observed by three independent, blinded raters in each class. To maintain consistency throughout the study, the blinded observers were responsible for observing and rating the same 6 children at specified intervals throughout the 12-hour testing period at each center" |
| Incomplete outcome data (attrition bias) | Low risk | "The intent-to-treat population included all randomized patients who took at least 1 dose of study medication and had at least 1 post-dose efficacy measurement"<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Low risk | No selective outcome reporting |
| Vested interest bias | High risk | "This study was funded by Novartis Pharmaceuticals Corporation and reports the following involvement: design and conduct of the study; collection, management, analysis, and interpretation of data; preparation, review, and approval of the manuscript"<br>Conflicts of interest: Dr. Muniz is an employee of Novartis Pharmaceuticals Corporation. He has no other relationships to disclose. Dr. Brams reports the following relationships: serves as speaker, consultant and Advisory Board member for Novartis and Shire; receives grant research support from Novartis, Shire and Eli Lilly. Dr. Mao reports the following relationships: speaker for Novartis, Eli Lilly, Bristol-Myers Squibb, AstraZeneca and Shire; consultant for Eli Lilly, Novartis and Shire; receives grant research support from Novartis. Mr. McCague is an employee of Novartis Pharmaceuticals Corporation. He has no other relationships to disclose. Ms. Pestreich is an employee of Novartis Pharmaceuticals Corporation. She has no other relationships to disclose. Dr. Silva reports the following relationships: none since 15 December 2006; before that, she was a speaker for Novartis, AstraZeneca and Janssen; received grant/research support from Novartis and Celgene |

*Murray 2011*

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| **Methods** | Phase IV, double-blind, randomised, cross-over, analogue classroom trials with 2 interventions<br>1. OROS methylphenidate<br>2. Placebo<br>**Phases**<br>1. Screening/washout phase: up to 28 days<br>2. Titration: up to 6 weeks<br>3. Double-blind assessment period, with the following subperiods<br>a. Open-label OROS methylphenidate: school day 1, OROS methylphenidate or placebo<br>b. Open-label OROS methylphenidate: ≥ 7 days<br>c. School day 2: OROS methylphenidate or placebo |

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| Participants | Number of participants screened: not stated<br>Number of participants included: 89. Participants randomly assigned to 1 of 2 possible drug condition orders: 68<br>Number of withdrawals before randomisation: 21<br>Number of withdrawals after randomisation: 2<br>Diagnosis of ADHD: DSM-IV-TR (combined (59%), hyperactive-impulsive (4%), inattentive (37%))<br>Age: mean 10.75 years (range 5 to 15)<br>IQ: > 80<br>Sex: 45 boys, 23 girls<br>Methylphenidate naive: 65%<br>Ethnicity: Caucasian (62%), African American (28%), Asian (not stated), Hispanic (not stated), other (10%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: anxiety (9%), depressive disorders (1%), learning disability (38%)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. 9 to 12 years of age<br>2. DSM-IV-TR diagnosis of ADHD<br>3. Parent-completed ADHD-RS-IV total or subscale scores ≥ 90th percentile for their age and sex<br>4. Attendance at a public or private school<br>5. Ability to read and understand English<br>6. Patients currently receiving ADHD medication must be inadequately managed on their current stimulant dose<br>7. To be eligible for the double-blind, randomised assessment period, participants had to reach their individualised OROS methylphenidate dose, defined as<br>a. ADHD Rating Scale, Fourth Edition (as scored by parent or guardian): ≤ 75th percentile for age and sex<br>b. ADHD Rating Scales, Fourth Edition (as scored by parent or guardian): between 75th and 85th percentiles for age and sex after either (1) a dose decrease for tolerability (1 dose decrease by 18 mg to a minimum of 18 mg/d was allowed), or (2) having reached a dosage of 54 mg/d<br>**Exclusion criteria**<br>1. Estimated full-scale IQ score ≤ 80, as determined by the 4-subtest version of the Wechsler Abbreviated Scale of Intelligence<br>2. Severe learning disability, defined as ≥ 2 SD below the mean score for their age on Gray Oral Reading Test, Test of Phonological Processing or Wechsler Individual Achievement Test, Second Edition<br>3. History or current diagnosis of a neurological or psychiatric disorder that might compromise the participant's welfare or ability to comply with study requirements<br>4. Inability to take or tolerate OROS methylphenidate<br>5. History of or current primary diagnosis of severe anxiety disorder, conduct disorder, psychotic disorders, pervasive developmental disorder, eating disorder, obsessive-compulsive disorder, sleep disorder, major depressive disorder, bipolar disorder, substance use disorder, chronic tic disorder, personal or family history of Tourette's syndrome<br>6. Weight < 3rd percentile for age<br>7. History of hospitalisation for treatment of a mood, anxiety or psychotic disorder<br>8. History of failed response to methylphenidate |

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| Interventions | Participants were randomly assigned to 1 of 2 possible drug condition orders of OROS methylphenidate and placebo<br>Mean OROS methylphenidate daily dosage: 47.6 mg<br>Administration schedule: once daily, morning<br>Average duration of OROS methylphenidate treatment: not stated<br>Duration of placebo intervention: 1 day<br>Washout before study initiation: up to 28 days<br>Medication-free period between interventions: no<br>Titration period: before randomisation, up to 6 weeks<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. Swanson, Kotkit, Agler, M-Flynn and Pelham Scale, observer-rated: 4 hours post dose (at the 2 laboratory days)<br>**Serious adverse events**<br>1. Serious adverse effects assessed at the 2 laboratory days and during open-label periods<br>**Non-serious adverse events**<br>1. Adverse effects, vital signs and body weight, at the 2 laboratory days<br>2. Adverse effects were collected during the open-label phase |
| Notes | Sample calculation: yes<br>Ethics approval: yes<br>**Key conclusion of study authors**<br>1. OROS methylphenidate improves performance on measures of attention and vigilance, behaviour and working memory in a laboratory school setting in 9- to 12-year-olds with ADHD<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; a history of failed response to methylphenidate was an exclusion criterion<br>Any withdrawals due to adverse events: 2<br>Email correspondence with study authors: June 2013 to June 2014. We have attempted to obtain supplemental efficacy data (Swanson, Kotkit, Agler, M-Flynn and Pelham Scale) and safety data from study authors. We are awaiting data from the Yale Open Data Access Project |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomised |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Low risk | Double-blind. Placebo and OROS methylphenidate were matched in appearance |
| Blinding of outcome assessment (detection bias) | Unclear risk | Double-blind |
| Incomplete outcome data (attrition bias) | High risk | 3 participants received OROS methylphenidate on both laboratory school days in error; therefore, only data for their first laboratory school assessment were included in the analyses<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Low risk | Outcomes reported according to protocol |
| Vested interest bias | High risk | Supported by Ortho-McNeil Janssen Scientific Affairs, LLC<br>Conflicts of interest: Several study authors had affiliations with pharmaceutical companies producing methylphenidate |

### *Musten 1997*

| Methods | Double-blind, randomised, placebo-controlled, cross-over trial with 3 interventions<br>1. Low dose of methylphenidate<br>2. High dose of methylphenidate<br>3. Placebo |
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| Participants | Number of participants screened: 109<br><br>Number of participants included: 54 met inclusion criteria; of these, the parents of 13 children refused methylphenidate treatment. In the final sample, 41 children were included. Participants were randomly assigned to 1 of the possible drug condition orders<br><br>Number of participants followed up: 31<br><br>Number of withdrawals: 10<br><br>Diagnosis of ADHD: DSM-III-R (subtype not stated)<br><br>**Regarding participants completing the study**<br><br>Age: mean 58.07 months (range 48 to 70)<br><br>IQ: mean 99.26<br><br>Sex: 26 boys, 5 girls<br><br>Methylphenidate naive: 93.5%<br><br>Ethnicity: not stated<br><br>Country: Canada<br><br>Setting: out-patient clinic<br><br>Comorbidity: oppositional defiant disorder (84%), conduct disorder (19%), mood disorder (0%), obsessive-compulsive disorder (0%), overanxious disorder (0%), somatisation disorder (0%), psychotic symptoms (0%)<br><br>Comedication: not stated<br><br>Sociodemographics: combined parental income Canadian $42,000: 2-parent home (74%), single-parent home (26%). Significant differences were observed between the treatment refused group (n = 13) and the treatment completed group (n = 31) on baseline symptoms assessed by Diagnostic Interview for Children and Adults-Parents; Swanson, Nolan and Pelham scale; and Conners' hyperactivity ratings<br><br>**Inclusion criteria**<br><br>1. 4 to 6 years of age<br>2. DSM-III-R diagnosis of ADHD (assessed by parent reports in the Diagnostic Interview for Children and Adults-Parents and a score > 1 of 8 on the 14 DSM-III-R items on the parent-rated Swanson, Nolan and Pelham Scale)<br>3. Standard score 80 on the Peabody Picture Vocabulary Test if unilingual English, 72 if bilingual<br>4. Mean score equal to 1.5 SD above age and sex means on the Hyperkinesis Index of Conners' Parent Rating Scale-Revised, as completed by the parent. Reports from day care providers or pre-schools were also required to indicate problem behaviours<br>5. Attention score < 88 seconds on the parent-supervised attention task. This criterion is 1.5 SD above the mean for attention on the task as performed by normal pre-school children<br>6. Parents and children fluent in English<br><br>**Exclusion criteria**<br><br>1. Attending or entering first grade at the time of assessment or for the duration of the study<br>2. Sensory or physical handicaps, developmental disorders (e.g. autism), neurological disease or obvious CNS dysfunction as assessed by a paediatrician<br>3. Had been receiving methylphenidate longer than 6 months, or daily dose was above dose specified in the research protocol |

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| Interventions | Participants were randomly assigned to 1 of 6 possible drug condition orders of low-dose (0.3 mg/kg) and higher-dose (0.5 mg/kg) methylphenidate and placebo<br>Administration schedule: twice daily, morning and lunch<br>Duration of each medication condition: 7 to 10 days<br>Washout before study initiation: 48 hours before screening assessment<br>Titration period: none<br>Treatment compliance: Treatment compliance was determined by counting the number of pills returned to the researcher at the end of each assessment week<br>Data on compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. Conners' Parent Rating Scale - Revised<br>**Non-serious adverse events**<br>1. Side Effects Rating Scale (Barkley 1990) rated by parent at the end of each treatment period |
| Notes | Sample calculation: no<br>Ethics approval: no information<br>**Comment from study authors**<br>1. Data on side effects are limited because of the age group of the population under investigation (4 to 6 years) - pre-schoolers cannot always articulate medication-related sensations, and this may have interfered with parents' ability to detect medication side effects<br>**Key conclusions of study authors**<br>1. Musten 1997 ( Musten 1997): Results suggest that methylphenidate can be used to improve the functioning of pre-school-aged children with ADHD, in a manner similar to their school-age counterparts<br>2. Firestone 1998 ( Musten 1997): Results indicate that methylphenidate has relatively low toxicity in pre-school children (over the first 7 to 10 days), that some behavioural changes that might be viewed as side effects of methylphenidate are actually normal behaviours or ADHD behaviours in pre-school children (e.g. sociability), that these "side-effect" behaviours are more common in pre-school than school-aged children, that some "side effects" of methylphenidate are associated with improvements in behaviour and that pre-school and school-aged children may experience different side effects of methylphenidate (e.g. mood changes, anxiety)<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: June 2013. Personal email correspondence with study author did not provide supplemental data and information as requested because of author's retirement, and because he has no access to the data because the study took place 15 years ago |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Treatment was presented in a fully randomised order as prepared by the hospital's pharmacy department |
| Allocation concealment (selection bias) | Low risk | Methylphenidate and placebo were placed in orange gelatin capsules to disguise taste differences |
| Blinding of participants and personnel (performance bias) | Low risk | All participants, research personnel and medical personnel were unaware of the order of medication conditions |
| Blinding of outcome assessment (detection bias) | Low risk | All participants, research personnel and medical personnel were unaware of the order of medication conditions |
| Incomplete outcome data (attrition bias) | High risk | Only data for children completing the entire study were analysed |
| Selective reporting (reporting bias) | Unclear risk | Not possible to get a copy of the protocol |
| Vested interest bias | Low risk | Supported by Health Canada grant<br>Conflicts of interest: none declared |

*Newcorn 2008*

| Methods | Twenty-site, randomised, placebo-controlled, double-blind, 6-week, parallel trial with 3 arms<br>1. Extended-release methylphenidate<br>2. Placebo<br>3. Atomoxetine |
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| Participants | Number of participants screened: 635<br>Number of participants included: 516<br>Number of participants randomly assigned: methylphenidate 220, placebo 74<br>Number of participants followed up: methylphenidate 180, placebo 57<br>Number of withdrawals: methylphenidate 40, placebo 17<br>DSM-IV diagnosis of ADHD (combined (67%), hyperactive-impulsive (1%), inattentive (32%))<br>Age: MPH mean 10.2, P mean 10.1 (range 6 to 16)<br>IQ: not stated<br>Sex: 211 boys, 83 girls<br>MPH-naive: 41%/121<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder (36%)<br>Comedication: not stated<br>Sociodemographics: not stated. No significant differences in baseline demographics were noted between the 2 groups<br>**Inclusion criteria**<br>1. Children 6 to 16 years of age<br>2. Meeting DSM-IV criteria for ADHD, any subtype<br>3. Symptom severity at entry was required to be ≥ 1.5 SD above US age and sex norms, as assessed by the ADHD Rating Scale, Fourth Edition - Parent Version<br>4. ADHD as the primary diagnosis<br>**Exclusion criteria**<br>1. Seizures, bipolar disorder, psychotic illness or pervasive developmental disorder<br>2. Taking concomitant psychoactive medications.<br>3. Anxiety or tic disorders or both<br>4. Previously treated with an adequate trial of methylphenidate or amphetamine and either did not experience at least some improvement in ADHD signs and symptoms (non-responders) or did experience intolerable adverse events |
| Interventions | Participants were randomly assigned to OROS methylphenidate or placebo<br>Mean methylphenidate dosage: 39.9 mg/d (SD 14.6) or 1.26 mg/kg/d (SD 0.55)<br>Administration schedule: single morning dose<br>Duration of intervention: 6 weeks<br>Titration period: none<br>Treatment compliance: not stated. Patients were required to discontinue any psychoactive medication for ≥ 5 days before entering the study |

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| Outcomes | **ADHD symptoms**<br>1. ADHD Rating Scale: observer-rated at baseline and at weeks 1, 3 and 6<br>2. Conners' Parent Rating Scale, ADHD Index: rated at baseline and at weeks 1, 3 and 6<br>3. General behaviour<br>**Quality of life**<br>1. Child Health Questionnaire: parent/teacher/observer-rated at baseline and at weeks 3 and 6<br>2. Serious adverse events<br>**Non-serious adverse events**<br>1. Open-ended questioning for adverse events and vital signs: observer-rated at baseline and at weeks 1, 3 and 6<br>2. No differences were observed in mean change in systolic blood pressure between placebo and methylphenidate<br>3. Weight loss was significantly greater with methylphenidate than with placebo |
| Notes | Sample calculation: no<br>Ethics approval: yes; approved by each site's ethical review board<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes<br>**Comments from study authors (limitations)**<br>1. It is likely that the methylphenidate dose was suboptimal for some adolescent participants<br>2. Restricting the dose of methylphenidate to 54 mg could also have limited response in some younger participants, as OROS methylphenidate sometimes is prescribed at doses higher than the FDA-recommended maximum for children<br>**Key conclusion of study authors**<br>1. Both treatments produced robust improvement, with a statistically significant difference in response favouring OROS methylphenidate<br>Email correspondence with study authors: November 2013 and January 2014. We requested additional data from study authors but never received them |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomly assigned |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | Study drugs were administered according to a double-dummy design. Identically appearing capsules were used |
| Blinding of outcome assessment (detection bias) | Low risk | Study drugs were administered according to a double-dummy design. Identically appearing capsules were used |
| Incomplete outcome data (attrition bias) | Low risk | NNTB was calculated for each treatment in relation to placebo and for atomoxetine in relation to methylphenidate. The number of participants was chosen to have 90% power to declare non-inferiority on the basis of a comparison of response rates, with a non-inferiority margin of 15%<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Low risk | All pre-specified outcomes of interest have been reported |
| Vested interest bias | High risk | Supported by Eli Lilly and Company<br>Conflicts of interest: Dr. Newcorn receives grant support from Eli Lilly and McNeil; is a consultant and/or advisor for Eli Lilly, McNeil, Shire, Novartis and Sanofi-Aventis; and is a member of Speakers' Bureaus for Eli Lilly and Novartis. Dr. Kratochvil receives grant support from Abbott, Cephalon, Eli Lilly, McNeil, Pfizer, Shire and Somerset; receives from Eli Lilly study medication for an NIMH (National Institute of Mental Health)-funded study; is a consultant for Abbott, AstraZeneca, Eli Lilly and Pfizer; and is a member of the Eli Lilly Speakers' Bureau. Dr. Casat receives research funding from Eli Lilly, Novartis and Abbott, and serves on an advisory board for Eli Lilly. Dr. Allen and Dr. Ruff are employees and shareholders of Eli Lilly. Dr. Michelson and Dr. Moore are former employees of Eli Lilly |

*Nikles 2006*

| Methods | Cross-over trial with 2 interventions<br>1. Short-acting stimulants (methylphenidate and dexamphetamine)<br>2. Placebo<br>Phases: Each trial included 3 pairs of treatment periods (n-of-1). Each pair contained the stimulant and the comparator stimulant or placebo. The child's doctor individualised the dosing, and the order of drugs was randomly assigned within each pair. Two treatment periods were included in a school week, and 2 days per treatment period (not including Wednesdays and weekends) |
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| Participants | Number of participants screened: 108 (85 boys, 21 girls). Two boys repeated n-of-1 trials; 22 (20%) trials were not completed<br><br>Number of participants included: 86. Participants were randomly assigned to 1 of 3 possible drug condition orders<br><br>Number of participants followed up: 86<br><br>Number of withdrawals: 10 (12%) trials were not completed<br>Diagnosis of ADHD: DSM-IV (subgroups not stated)<br><br>Age: median 10 years (range 5 to 16)<br><br>IQ: not stated<br><br>Sex: 66 boys, 18 girls<br><br>Methylphendaite-naive: 36 were taking methylphenidate, 47 dexamphetamine, 3 unknown pre-trial medication<br><br>Ethnicity: All were Caucasian (Nikles 2007 in Nikles 2006)<br><br>Country: Australia<br><br>Setting: out-patient clinic<br><br>Comorbidity: not stated<br><br>Comedication: not stated<br><br>Sociodemographics: caregiver's occupation: full-time work 21%, part-time or casual work 33%, unemployed or retired 5%, unpaid homemakers 25%, other 10%, unknown 5%<br><br>**Inclusion criteria**<br><br>1. Clinical diagnosis of ADHD according to DSM-IV criteria<br>2. Stable on an apparently optimal dose of stimulant<br>3. Informed consent from parent and school teacher (children 12 years of age provided assent)<br>4. 5 to 16 years of age<br>5. Uncertainty about treatment effectiveness<br><br>**Exclusion criteria**<br><br>1. No teachers available and willing to provide observations |
| Interventions | Participants were randomly assigned to 1 of 3 possible drug condition orders of individual doses of methylphenidate, dexamphetamine and placebo<br><br>Mean methylphenidate dosage: not stated<br>Administration schedule and time points: different for different individuals, as this is a series of n-of-1 trials<br><br>Duration of each medication condition: 2 days each of methylphenidate and placebo per week<br><br>Washout before study initiation: 40 hours (from 4:00 PM Tuesday to 8:00 AM Thursday) and 64 hours (4:00 PM Friday to 8:00 AM Monday)<br><br>Titration period: not stated, but all were stabilised on an "optimal" dose of stimulant, initiated before randomisation<br><br>Treatment compliance: not stated |

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| Outcomes | **ADHD symptoms**<br>First 41 participants used at the end of each treatment period<br>1. Conners' Teacher and Parent Self Reported - Revised, short form<br>2. Conners-Wells Adolescent Rating Scales<br>From 42nd participant onwards used at the end of each treatment period<br>1. Changed to ADHD du Paul Rating Scale IV parent and teacher questionnaires, "because they were less expensive but adequately reliable and valid for monitoring response to treatment"<br>2. Conners-Wells Adolescent Rating Scales<br>**Non-serious adverse events**<br>1. Assessment of adverse effects by parent and teacher during and at the end of each treatment period |
| Notes | Sample calculation: irrelevant<br>Ethics approval: yes<br>**Key conclusion of study authors**<br>1. Attention deficit hyperactivity disorder n-of-1 trials can be implemented successfully by mail and telephone communication. This type of trial can be valuable in clarifying treatment effect when it is uncertain, and in this series, treatments had a noticeable impact on short-term management<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: yes (n = 1, insomnia and depression)<br>**Comments from review authors**<br>1. This study was more about the use of n-of-1 trials in determining optimal drug treatment in cases for which this was uncertain<br>2. Nikles 2007 (in Nikles 2006) does not add any relevant outcome data |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "The order of drugs was randomly assigned within each pair"; "There were three pairs of treatment periods, with the order of drugs randomly assigned by a computer-generated randomisation schedule within each" |
| Allocation concealment (selection bias) | Low risk | See above |
| Blinding of participants and personnel (performance bias) | Low risk | "Patients, parents, doctors, and the research assistant were all blinded to medication order" |
| Blinding of outcome assessment (detection bias) | Low risk | "A hospital pharmacy encapsulated the medication (crushing of tablets and production of identical capsules containing either medication or placebo)"; "Active medication was encapsulated and identical placebo capsules were produced by a hospital pharmacy" |
| Incomplete outcome data (attrition bias) | Unclear risk | Not stated |
| Selective reporting (reporting bias) | Low risk | All outcomes are reported |
| Vested interest bias | Unclear risk | No information<br>Conflicts of interest: Study authors have indicated that they have no financial relationships relevant to this article to disclose |

*Oesterheld 1998*

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| **Methods** | Cross-over trial with 3 interventions<br>1. Methylphenidate<br>2. Lactose placebo<br>3. Vitamin C placebo<br>Phases: Five-day trial lasting for 3 consecutive weeks, with 2 medication-free days between phases |
| **Participants** | Number of participants screened: 30<br>Number of participants included: 4. Participants were randomly assigned to different possible drug condition orders of methylphenidate, lactose placebo and vitamin C placebo<br>Number followed up: 4 (2 boys, 2 girls)<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-IV (combined (66.7%), hyperactive-impulsive (0%), inattentive (33.3%))<br>Age: mean 8.25 years (range 5 to 11)<br>IQ: mean 72.5 (range 63 to 79)<br>Methylphenidate naive: 100%<br>Ethnicity: Native American (100%)<br>Country: USA<br>Setting: out-patient clinic (residential school)<br>Comorbidity: not stated<br>Comedication: no<br>Sociodemographics: not living with family<br>**Inclusion criteria**<br>1. Native Americans<br>2. 5 to 12 years of age<br>3. Residing at the residential school within 6 months<br>4. DSM-IV ADHD diagnosis<br>5. Diagnosis of foetal alcohol syndrome, partial foetal alcohol syndrome or alcohol-related birth defects according to criteria from the Fetal Alcohol Study Group of the Research Society of Alcoholism (1989)<br>**Exclusion criteria**<br>1. Pregnancy<br>2. Lactose intolerance<br>3. Prior psychotropic medication use<br>4. Bipolar disorder<br>5. Acute and chronic medical or neurological disorders<br>6. Current history of seizures<br>7. Lead levels > 9 mcg/dL<br>8. Height and weight at or below 3rd percentile<br>9. IQ < 60 |
| **Interventions** | Participants were randomly assigned to different possible drug condition orders of methylphenidate (0.6 mg/kg), lactose placebo and vitamin C placebo<br>Mean methylphenidate dosage: not stated (range 10 mg/d to 17.5 mg/d)<br>Administration schedule: 7:30 AM, 11:00 AM and 2:00 PM<br>Duration of each medication condition: 5 days for 3 consecutive weeks<br>Washout before study initiation: not stated<br>Medication-free period between interventions: 2 days<br>Titration period: none. Fixed dose. Initiated before/after randomisation<br>Treatment compliance: medication given by nurse (directly observed treatment) |

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| Outcomes | **ADHD symptoms**<br>1. Conners' Parent Rating Scale (48 items) and Conners' Teacher Rating Scale (39 items): both completed daily in each trial period by caretakers and teachers, respectively<br>**Non-serious adverse events**<br>1. Barkley Side Effects Questionnaire was completed by both teacher and caretaker before treatment |
| Notes | Sample calculation: no<br>Ethics approval: yes; Human Subjects Committee of the University of South Dakota's School of Medicine and the Research Committee of the Black Hills Children's Home Society<br>**Key conclusion of study authors**<br>1. When fetal alcohol syndrome and ADHD co-exist, ADHD symptoms of native children may respond to standard treatment with methylphenidate without major side effects<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Comment from review authors**<br>1. Methylphenidate was prepared to the nearest 2.5 mg using regular 5 mg and 10 mg methylphenidate tablets that had been crushed and placed within gelatin capsules, which may result in uncertainty of actual dose administered<br>Email correspondence with study authors: not able to find email addresses for study authors because information is missing from the paper. Not possible to find on the Internet, etc. |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The order of the trials was randomly determined |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Low risk | School caretakers, nurses, teachers and researchers were blinded as to whether treatment consisted of placebo or active agent. All agents were placed in identical capsules |
| Blinding of outcome assessment (detection bias) | Low risk | On each day of each trial, a teacher, blinded to evaluation data, rated the child's behaviour in school using Conners' Teacher Rating Scale (39 items). The caregiver, blinded to evaluation data, completed Conners' Parent Rating Scale (48 items) on a daily basis. School caretakers, nurses, teachers and researchers were blinded as to whether treatment consisted of placebo or active agent. All agents were placed in identical capsules |
| Incomplete outcome data (attrition bias) | Low risk | No drop-outs<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | No protocol identified |
| Vested interest bias | Low risk | Research was supported by a University of South Dakota/USF-Mini Grant<br>Conflicts of interest: none declared |

*Overtoom 2003*

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| **Methods** | Double-blind, randomised, cross-over trial with 4 interventions<br>1. Methylphenidate<br>2. Desipramine<br>3. L-dopa<br>4. Placebo |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 16. Participants were randomly assigned to 1 of the possible drug condition orders<br>Number of participants followed up: 16 (all boys)<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-III-R (combined (100%))<br>Age: mean 10.4 years (range 7 to 12)<br>IQ: 95.4<br>Methylphenidate naive: 0 (0%)<br>Ethnicity: not stated<br>Country: the Netherlands<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder (n = 6), comorbid anxiety disorder (n = 1), specific developmental disorders (n = 3)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Diagnosis of ADHD according to DSM-III-R criteria<br>2. Scored in the clinical range on both the Child Behavior Checklist Inattention factor (t scores > 70, i.e. 98th percentile) and Conners' Teacher Rating Scale Hyperactivity factor (mean factor score > 2.2)<br>**Exclusion criteria**<br>1. Diagnosis of tic disorder or pervasive developmental disorder<br>2. Abnormal values (1 week before medication study) of ECG and blood measures that contraindicate desipramine medication<br>3. Family history of severe heart problems |
| **Interventions** | Participants were randomly assigned to 1 of the possible drug condition orders of methylphenidate, desipramine, L-dopa and placebo<br>Mean methylphenidate dosage: 15 mg<br>Administration schedule: once, in the afternoon<br>Duration of each medication condition: 1 day<br>Washout before study initiation: 3 days before for methylphenidate users<br>Medication-free period between interventions: not stated<br>Titration period: none<br>Treatment compliance: 100% |
| **Outcomes** | **Non-serious adverse events**<br>1. Sleepiness reported by 1 participant |

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| **Notes** | Sample calculation: no<br>Ethics approval: yes<br>**Key conclusions of study authors**<br>1. Inhibition of performance improved under desipramine but not under methylphenidate or L-dopa. Response time to the stop signal was marginally shortened after intake of desipramine<br>2. Methylphenidate decreases omission and choice errors and causes faster reaction times in trials without the stop tone<br>3. No effects of L-dopa whatsoever were noted<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; all participants were already stable on methylphenidate |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomised |
| Allocation concealment (selection bias) | Unclear risk | Not specified |
| Blinding of participants and personnel (performance bias) | Unclear risk | "A double-blind randomised design was used" |
| Blinding of outcome assessment (detection bias) | Unclear risk | Double-blind |
| Incomplete outcome data (attrition bias) | Low risk | No drop-outs<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | No protocol available |
| Vested interest bias | Low risk | Research supported by Netherlands Organisation for Scientific Research (NWO) Grant 575-63-082<br>Conflicts of interest: not declared |

*Palumbo 2008*

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| **Methods** | Multi-centre, randomised, double-blind, 16-week, parallel trial with 2 × 2 factorial design<br>1. Methylphenidate alone<br>2. Methylphenidate and clonidine<br>3. Clonidine alone<br>4. Placebo<br>Two successive 4-week titration periods followed by an 8-week maintenance period |
| **Participants** | Number of participants screened: 205<br>Number of participants included: 122 (98 boys, 24 girls)<br>Number randomly assigned: methylphenidate 29, placebo 30, methylphenidate + clonidine 32, clonidine 31<br>Number followed up: methylphenidate 18, placebo 10, methylphenidate + clonidine 24, clonidine 31<br>Number of withdrawals: methylphenidate 11, placebo 20, methylphenidate + clonidine 8, clonidine 5<br>DSM-IV diagnosis of ADHD (combined (76%), hyperactive-impulsive (4%), inattentive (20%))<br>Age: mean 9.5 (range not reported) |

IQ: > 70

Methylphenidate-naive: 57 (46.7%)

Ethnicity: Caucasian (77.9%), African American (10.7%), Hispanic (6.6%), other (4.9%)

Country: USA

Setting: out-patient clinic

Co-morbidity: oppositional defiant disorder (47%), conduct disorder (9%)

Co-medication: no. Protocol-based behavioural interventions

Sociodemographics: not stated. Participant groups were similar except for a higher percentage of whites in the clonidine group and some minor differences with regard to family history of ADHD and tics

**Inclusion criteria**

1. Children 7 through 12 years of age in school
2. DSM-IV ADHD, any subtype: indication of a sufficient number of ADHD symptoms on the Disruptive Behavior Disorders Rating Scale as rated by a teacher
3. Rating of ADHD symptoms above specified cutoff scores (boys: grade 2 to 3 = 10; grade ≥ 4 = 9; girls: grade 2 to 3 = 7, grade ≥ 4 = 6) on the Iowa Conners' Teacher Rating Scale
4. Indication of the presence of sufficient ADHD symptoms at home on the Iowa Conners' Parent Rating Scale
5. Investigators rating of global functioning on the Child Global Assessment Scale (CGAS) ≤ 70, with difficulty evident in ≥ 2 areas, such as school and home
6. ADHD must be viewed as worthy of treatment with medications, as judged by the parent and the site investigator
7. Informed consent/assent signed
8. Designated school for each participant agrees to participate in the study by completing all required questionnaires and following all specified procedures
9. Child must be able to swallow the tablets and capsules used in this study

**Exclusion criteria**

1. Evidence of a tic disorder
2. Major depression
3. Pervasive developmental disorder
4. Autism
5. Psychosis
6. Mental retardation
7. Anorexia nervosa
8. Bulimia
9. Serious cardiovascular (e.g. significant hypotension, congenital heart disease) or other medical disorder that would preclude safe use of methylphenidate or clonidine
10. Impaired renal function or pregnancy
11. Family history of long QT syndrome, cardiomyopathy or premature (age 45 years) sudden death
12. Prolonged QTc interval (> 440 milliseconds), high-grade ventricular ectopy, atrioventricular block beyond first degree, bundle branch block, intraventricular conduction block (> 100 milliseconds), pacemaker rhythm or HR < 60 bpm on the ECG, significant hypotension, cardiomyopathy, congenital heart disease, aortic or pulmonary stenosis, history of syncope
13. Blood pressure ≥ 2 SD above or below the age- and sex-adjusted mean
14. Stimulants had to be discontinued ≥ 2 weeks before enrolment
15. Any other psychotropic medications, anxiolytics or hypnotics had to be discontinued ≥ 6 weeks before enrolment

Previous use of methylphenidate or clonidine was permitted

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| Interventions | Participants were randomly assigned to immediate-release methylphenidate or placebo<br>Mean methylphenidate dosage: 0.76 ± 0.54 mg/kg/d (30.2 ± 18.9 mg/d (methylphenidate-only group) and 25.4 ± 18.2 mg/d (methylphenidate + clonidine))<br>Administration schedule: 1 to 3 times daily (morning, noon and afternoon)<br>Duration of intervention: 12 to 16 weeks<br>Washout before study initiation: 2 weeks<br>Titration period: 8-week flexible-dose titration period (4 weeks for clonidine, then 4 weeks for methylphenidate) initiated after randomisation<br>Maintenance period of optimal dose: 8 weeks<br>Treatment compliance: monitored using pill counts (results of monitoring not stated) |
| Outcomes | **ADHD symptoms**<br>1. ADHD Rating Scale (ADHD RS-IV, 18-item): child psychiatrist-rated at baseline and at 16 weeks<br>2. ASQ: teacher-rated at baseline and at 4, 8, 12 and 16 weeks<br>3. ASQ: parent-rated at baseline and at 4, 8, 12 and 16 weeks<br>4. IOWA Conners' Rating Scale: teacher-rated at baseline and at 4, 8, 12 and 16 weeks<br>**Quality of life**<br>1. Child Global Assessment Scale: rated at baseline and at 4, 8, 12 and 16 weeks<br>**Non-serious adverse events**<br>1. Pittsburgh Side Effects Rating Scale (20 items, modified from the original 13 items to include potential clonidine side effects): parent- and teacher-rated at baseline and at 4, 8, 12 and 16 weeks.<br>2. Spontaneous self reports of adverse events: parent- and participant-rated at baseline and at 4, 8, 12 and 16 weeks, or by telephone calls conducted between visits<br>3. Weight, ECG, supine and standing blood pressures and pulse at visits 4, 8, 12 and 16 |

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| Notes | Sample calculation: yes; sample size of 140 participants (35 per treatment group) was determined to provide between 80% and 90% power to detect a group difference (effects of clonidine)<br>Ethics approval: yes; approved by the institutional review board at each site<br>**Comments from study authors**<br>1. Overall, findings should be viewed cautiously in the light of the relatively small sample size and differential rates of attrition across groups<br>2. Findings are limited by the exclusion of children with certain co-morbid disorders such as mood and anxiety disorders, known cardiac problems or abnormal ECGs<br>3. Also, given that all participants received psychoeducational and behavioural interventions as part of the protocol, these results may be limited to settings in which such behavioural interventions are applied<br>4. Study relied largely on parent and teacher questionnaires to identify possible side effects of medications. However, such rating scales may overestimate rates of medication side effects because sometimes such complaints reflect other factors, such as underlying conditions or co-morbid psychopathology<br>**Key conclusions of study authors**<br>1. Based on Conners' Teachers Abbreviated Symptom Questionnaire; methylphenidate offers best combination of efficacy and tolerability for ADHD<br>2. Clonidine, used alone or with methylphenidate, appears safe and well tolerated in childhood ADHD<br>3. Study provides evidence that measures of quality of life for the family are sensitive to pharmacological treatment for ADHD<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: Moderate to severe adverse events were cited as a reason for withdrawal in 8 participants: methylphenidate + clonidine 5, clonidine 2, methylphenidate 1<br>Methylphenidate + clonidine: irritability (n = 1), tearfulness and irritability (n = 1), headaches (n = 1), itching (n = 1), asymptomatic ECG abnormalities (prolonged QTc) (n = 1) Methylphenidate: tachycardia and palpitations (n = 1)<br>Email correspondence with study authors: March 204 to June 2014. We attempted to obtain supplemental efficacy data from the study authors |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computer-generated randomisation plan included stratification by centre (investigator) and by sexual maturity status (Prepubertal: Tanner I-II, Pubertal: Tanner III-V) |
| Allocation concealment (selection bias) | Low risk | Only the programmer in the Biostatistics Centre and the pharmacist knew the allocation |
| Blinding of participants and personnel (performance bias) | Low risk | Methylphenidate (or matching placebo) powder packaged in gelatin capsules |
| Blinding of outcome assessment (detection bias) | Low risk | All investigators, study co-ordinators, teachers, parents and children were blinded to treatment assignments |
| Incomplete outcome data (attrition bias) | Unclear risk | Statistical analyses were performed according to the ITT principle, and last available observations were carried forward and imputed when needed for both efficacy and safety measures. However, only data from the ADHD Rating Scale for children who completed the titration period were analysed |
| Selective reporting (reporting bias) | Low risk | Protocol published. All pre-specified outcomes of interest have been reported |
| Vested interest bias | High risk | This project was supported by NIH (National Institutes of Health) and NINDS (National Institute of Neurological Disorders and Stroke)<br>Conflicts of interest: Some study authors are on the ADHD Advisory Board and the Speakers' Bureau of; are scientific consultants or principal or site investigators for; and/or have received educational or funding support from several pharmaceutical companies |

*Pearson 2013*

| Methods | Four-week, cross-over trial with 2 interventions<br>1. Methylphenidate<br>2. Placebo<br>**Phases**<br>1. 1-week placebo<br>2. 1-week low-dose methylphenidate<br>3. 1-week medium-dose methylphenidate<br>4. 1-week high-dose methylphenidate |
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| Participants | Number of participants screened: 94<br>Number of participants included: 24 (19 boys, 5 girls). Participants were randomly assigned to 1 of 4 possible drug condition orders<br>Number of participants followed up: 24<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-IV (combined 19, inattentive 5)<br>Age: mean 8.8 years (range 7.1 to 12.7)<br>IQ: mean 85 (range 46 to 112)<br>Methylphenidate naive: 13<br>Ethnicity: Caucasian (n = 13), African American (n = 4), Asian (n = 1), Hispanic (n = 5), other (n = 1)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder (n = 5), obsessive-compulsive disorder (n = 2), separation anxiety disorder (n = 1)<br>Comedication: yes<br>Sociodemographics: Hollingshead 4 Factor Social Class 1.7 (0.9); Hollingshead 4 Factor SES Score 52.3 (10.8)<br>**Inclusion criteria**<br>1. Not clearly stated<br>**Exclusion criteria**<br>1. Serious neurological disorders (e.g. stroke, seizures)<br>2. Down syndrome<br>3. Fragile X syndrome<br>4. Tourette's syndrome<br>5. Psychosis<br>6. Mood disorders |
| Interventions | Participants were randomly assigned to 1 of 3 possible drug condition orders of (low, medium and high) methylphenidate and placebo<br>Mean methylphenidate dosage: low = 0.21 mg/kg; medium = 0.35 mg/kg; high = 0.48 mg/kg<br>Administration schedule: b.i.d.<br>Duration of each medication condition: 1 week<br>Washout before study initiation: yes<br>Medication-free period between interventions: not stated<br>Titration period: 1 week before randomisation<br>Treatment compliance: "Parents completed a medication administration form, were asked about missing or late doses at weekly interviews and teachers were asked as well. Forms were verified by number of pills in returned vials. Families were asked again in case of discrepancy. Parents and teachers were also asked about unanswered items om questionnaires" |

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| Outcomes | **ADHD symptoms**<br>1. Conners' Parent Rating Scale - Revised<br>2. Conners' Teacher Rating Scale - Revised<br>3. Swanson, Nolan and Pelham Scale, Fourth Edition<br>4. ADD/H Comprehensive Teacher Rating Scale (ACTeRS), Parent and Teacher Forms<br>**Non-serious adverse events**<br>1. Nine of 24 parents (38%) reported insomnia at the high dose, compared with 5 (21%) while taking placebo<br>2. Nine parents reported loss of appetite at the high dose, compared with only 1 during placebo |
| Notes | Sample calculation: no<br>Ethics approval: yes<br>**Key conclusions of study authors**<br>1. It is ideal for clinicians to assess behavioural response in both home and school settings when titrating methylphenidate treatment for children with ASD and significant ADHD symptoms<br>2. It is important to monitor each child for side effects (e.g. increases in stereotypies or irritability)<br>3. Methylphenidate formulations are efficacious and well tolerated in children with ASD and significant ADHD symptoms<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: no |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | We used the Digram balanced randomisation method that Dr. David Lane (a professor of both psychology and statistics at nearby Rice University) used to create the 8 balanced drug dose orders to which our 24 participants were assigned |
| Allocation concealment (selection bias) | Low risk | Central allocation |
| Blinding of participants and personnel (performance bias) | High risk | One-week, single-blind, "lead-in-dosing"; all study personnel with participant contact were blind with respect to dosages given during the drug trial |
| Blinding of outcome assessment (detection bias) | Low risk | "The study medication was prepared by the University of Texas Psychiatry Research Pharmacy: the Ritalin LA beads were mixed with (inert) placebo beads and placed in two opaque gelatin capsules, and the white generic IR-MPH was crushed and mixed with cornstarch and placed in two size 1 gelatin capsules" |
| Incomplete outcome data (attrition bias) | High risk | Blank was left for missing data<br>Selection bias: yes; exclusion of placebo responder during single-blind placebo washout week |
| Selective reporting (reporting bias) | Low risk | All outcomes are reported |
| Vested interest bias | Low risk | Funded by grant number MH072263 from National Institute of Mental Health (NIMH)<br>Conflicts of interest: none declared&& |

### *Pelham 1989*

| Methods | Cross-over trial with 2 interventions<br>1. Methylphenidate<br>2. Placebo<br>**Phases**<br>1. No clear method description: "The procedure was double-blind placebo-controlled in which each child received, in random order with condition varied daily, placebo b.i.d. and 0.3 mg MPH/kg b.i.d." - "5 to 9 days of data were gathered" |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 24. Participants were randomly assigned to 1 of 2 possible drug condition orders; condition varied daily: placebo b.i.d. and 0.3 mg MPH/kg b.i.d.<br>Number followed up: not stated<br>Number of withdrawals: not stated<br>Diagnosis of ADHD: DSM-III (combined (not stated), hyperactive-impulsive (19/24), inattentive (2/24))<br>Age: mean not reported (range: boys 5 years 6 months to 11 years; girls 5 years 8 months to 11 years 3 months)<br>IQ: boys 100.8 (SD 14.23), girls 104.0 (SD16.52)<br>Sex: 12 boys, 12 girls<br>Methylphenidate naive: not stated<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic (summer treatment programme)<br>Comorbidity: attention deficit disorder (1/24), conduct disorder (5/24), oppositional defiant disorder (15/24), learning disability (6/25)<br>Comedication: yes; other doses of stimulants reported but not on study days<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. None stated<br>**Exclusion criteria**<br>1. Children who were mentally retarded and those who had gross neurological disorders were not included in the study |
| Interventions | Participants were randomly assigned to 1 of 2 possible drug condition orders of 0.3 mg/kg methylphenidate and placebo. "Each child received, in random order with condition varied daily, placebo b.i.d. and 0.3 mg MPH/kg b.i.d."<br>Mean methylphenidate dosage: boys 9.8 mg (range 5.3 to 16.9), girls 9.5 mg (range 5.2 to 13.1)<br>Administration schedule: at breakfast and at lunchtime<br>Duration of each medication condition: not stated<br>Washout before study initiation: not stated<br>Medication-free period between interventions: no<br>Titration period: none<br>Treatment compliance: no information |
| Outcomes | **ADHD symptoms**<br>1. Abbreviated Conners' Teacher Rating Scale (CTRS): 1 to 3 times per condition<br>2. Revised Behaviour Problem Checklist: counsellor-rated, 1 to 3 times per condition<br>3. IOWA Conners' Teacher Rating Scale (IOWA CTRS)<br>**General behaviour**<br>1. Daily frequencies (following rules, non-compliance, positive peer behaviours, conduct problems, negative verbalisations, numbers of time-outs per day): daily<br>2. Time-out: daily<br>3. Classroom measures, teacher recorded: daily<br>4. Daily report card<br>5. Observed peer interaction using modification of RECESS code: daily |

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| **Notes** | Sample calculation: no<br>Ethics approval: no information.<br>**Comment from study authors**<br>1. Study involved only 12 boys and 12 girls; 1 dose of methylphenidate in the context of a highly structured summer programme: results must be considered preliminary<br>**Key conclusions of study authors**<br>1. Results revealed equivalent and beneficial effects of methylphenidate for both boys and girls<br>2. Methylphenidate therefore would appear to be a treatment that is as useful for girls with ADD as for boys with ADD<br>**Comments from review authors**<br>1. Data reported from this study cannot be considered robust<br>2. No information on ethics committee approval, on randomisation, on primary endpoint (multiple endpoints), on sample size calculation, on safety, etc. Concomitant behavioural treatment was provided, but no details are given in the Methods section<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no information<br>Any withdrawals due to adverse events: no information<br>Email correspondence with study authors: October 2014. We received no supplemental information/data from study authors. We asked authors whether this article was part of the Johnston 1988 study but received no response, so we extracted the data as from 2 separate studies |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Each child received, in random order with condition varied daily, placebo and methylphenidate |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Low risk | Active medication and placebo were disguised in gelatin capsules and were pre-packaged in individual, dated envelopes |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not stated |
| Incomplete outcome data (attrition bias) | Unclear risk | Not stated |
| Selective reporting (reporting bias) | Unclear risk | Not stated |
| Vested interest bias | Unclear risk | Not stated |

### *Pelham 1990a*

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| **Methods** | Double-blind, placebo-controlled, cross-over trial<br>1. Immediate-release methylphenidate<br>2. Sustained-release methylphenidate<br>3. Sustained-release dextroamphetamine<br>4. Pemoline<br>5. Placebo |

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| Participants | Number of participants screened: not stated<br>Number of participants included: 22 (all boys). Participants were randomly assigned to 1 of the possible drug condition orders<br>Number of participants followed up: 22<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-III-R (subtype not stated)<br>Age: mean 10.39 years (range 8.08 to 13.17)<br>IQ: mean 105.68<br>Methlyphenidate-naive: not stated<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic (summer treatment programme)<br>Comorbidity: oppositional/defiant disorder (n = 9), conduct disorder (n = 4), "suggesting the presence of a learning disability", but IQ > 80 (n = 13)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criterion**<br>1. Participating in the Summer Treatment Program of the 1988 Western Psychiatric Institute and Clinic Attention Deficit Disorder Program<br>**Exclusion criteria**<br>1. Not stated |
| Interventions | Participants were randomly assigned different possible drug condition orders of methylphenidate (10 mg b.i.d., SR-20 q.a.m.) and placebo<br>Mean methylphenidate dosage: immediate-release methylphenidate 10 mg = 0.29 mg/kg<br>Administration schedule: twice daily: immediate-release methylphenidate twice daily: morning and lunchtime; sustained-release methylphenidate once daily: morning<br>Duration of each medication condition: 1 day, but in total 3 to 6 days<br>Washout before study initiation: none<br>Medication-free period between interventions: not stated<br>Titration period: no<br>Treatment compliance: none<br>All completed study: not stated |
| Outcomes | **ADHD symptoms**<br>1. Teacher ratings on the Abbreviated Conners' Teacher Rating Scale: 2 to 4 times in each medication condition<br>2. Counsellor ratings on the Abbreviated Conners' Teacher Rating Scale: 2 to 4 times in each medication condition<br>**Non-serious adverse events**<br>1. Parent, teacher and counsellor side effect checklist: at least once per condition |

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| **Notes** | Sample calculation: no<br>Ethics approval: not stated<br>**Comments from study authors**<br>1. It should be noted that the results we have presented apply to the short-term effects of these medications<br>2. Results of this study might not predict long-term response to the initial dose<br>**Key conclusions of study authors**<br>1. The 3 long-acting stimulants and immediate-release methylphenidate were superior to placebo<br>2. All 4 had similar time courses with effects from 1 to 9 hours after ingestion<br>3. Individual differences in drug responsivity were noted<br>**Comments from review authors**<br>1. The article states that comorbidity is diagnosed according to DSM-III-R, but study authors do not mention whether the ADHD diagnosis is based on DSM-III-R<br>2. We have chosen in our data extraction to assume that this is so<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: no<br>Email correspondence with study authors: January 2014. No contact made through author correspondence |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomised |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Low risk | Active medication and placebo were disguised in gelatin capsules and were pre-packaged in individual daily pill reminders |
| Blinding of outcome assessment (detection bias) | Unclear risk | Double-blind |
| Incomplete outcome data (attrition bias) | Low risk | No<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Unclear risk | No protocol available |
| Vested interest bias | Unclear risk | Not stated<br>Conflicts of interest: not stated |

### *Pelham 1993a*

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|---|---|
| **Methods** | Cross-over trial with 2 interventions<br>1. Methylphenidate 0.3 mg/kg and 0.6 mg/kg<br>2. Placebo<br>Phases: 3 |

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| Participants | Number of participants screened: not stated<br>Number of participants included: 31. Participants were randomly assigned to 1 of 3 possible drug condition orders<br>Number of participants followed up: 31 (all boys)<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-III-R (therefore no subtype)<br>Age: mean 98.8 months (range 5.42 to 9.92)<br>IQ: mean 110.7 (range not stated)<br>Methylphenidate naive: not stated<br>Ethnicity: Caucasian (93.5%), African American (6.5%)<br>Country: USA<br>Setting: hospital (Summer Treatment Program)<br>Comorbidity: oppositional defiant disorder (32%), conduct disorder (48%)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criterion**<br>1. Boys with ADHD attending a Psychiatric Institute and Clinic Summer Treatment Program<br>**Exclusion criteria**<br>1. None described |
| Interventions | Participants were randomly assigned to 1 (of not stated) possible drug condition order of 0.3 mg/kg and 0.6 mg/kg methylphenidate and placebo<br>Mean methylphenidate dosage (SD): low 8.1 mg (range 5 to 15); high 16.0 mg (range 10 to 22.5)<br>Administration schedule: twice a day morning and midday; conditions were changed daily over 6 weeks<br>Duration of each medication condition: 2 weeks overall (individual treatment condition 1 day)<br>Washout before study initiation: not described<br>Titration period: none<br>Treatment compliance: not reported |
| Outcomes | **ADHD symptoms**<br>1. Teachers rated inattention/overactivity daily with the IOWA Conners' Teacher Rating Scale |
| Notes | Sample calculation: no<br>Ethics approval: not stated<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Key conclusion of study authors**<br>1. Relatively small incremental value was gained by the higher dose of medication or by the addition of behaviour modification compared with the effects of the low dose of methylphenidate<br>Email correspondence with study author: June 2014. Emailed study author to ask for additional information but have received no response |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Referred to as a randomised study but sequence generation not described |
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Blinding of participants and personnel (performance bias) | Low risk | Capsules were identically packaged |
| Blinding of outcome assessment (detection bias) | Unclear risk | Referred to as double-blind but not described |
| Incomplete outcome data (attrition bias) | Low risk | Appears to be 100% follow-up |
| Selective reporting (reporting bias) | Unclear risk | Protocol not identified |
| Vested interest bias | Unclear risk | None reported<br>Conflicts of interest: no information |

*Pelham 1999*

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|---|---|
| **Methods** | Six-week, within-participant, double-blind, placebo-controlled, cross-over design<br>1. Methylphenidate<br>2. Placebo<br>3. D- and L-AMPH<br>Phases: 5 |
| **Participants** | Number of participants screened: 26<br>Number of participants included: 25 (21 boys, 4 girls). Participants were randomly assigned to 1 of 4 possible drug condition orders<br>Number of participants followed up: 23<br>Number of withdrawals: 2<br>Diagnosis of ADHD: DSM-IV (subtype not stated)<br>Age: mean 9.6 years (range 5.8 to 12.7)<br>IQ: average intelligence<br>Methylphenidate naive: not stated<br>Ethnicity: Caucasian (88%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder (n = 13), conduct disorder (n = 8)<br>Comedication: not stated<br>Sociodemographics: "Median family income was US $40 000, with incomes ranging widely (from US $10 000 per year to US $100 000 per year)"<br>**Inclusion criteria**<br>1. Not stated<br>**Exclusion criteria**<br>1. Not stated |

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| Interventions | Participants were randomly assigned to 1 of 2 possible drug condition orders of 10 mg or 17.5 mg methylphenidate and placebo<br>Administration schedule: 2 time points<br>Duration of each medication condition: 5-day period<br>Washout before study initiation: not stated<br>Medication-free period between interventions: no<br>Titration period: none initiated before/after randomisation<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. IOWA Conners' Rating Scale (parent)<br>2. IOWA Conners' Rating Scale (teacher)<br>**Non-serious adverse events**<br>1. Tics |
| Notes | Sample calculation: not stated<br>Ethics approval: not stated<br>**Key conclusions of study authors**<br>1. "Both drugs were routinely superior to placebo and produced dramatic improvements in rates of negative behaviour, academic productivity, and staff/parent ratings of behaviour"<br>2. DEX-AMPH AMPH produced greater improvement than methylphenidate. Doses of DEX-AMPH AMPH used were more potent than those of methylphenidate<br>3. Both drugs produced low levels of side effects. 25% of study participants were judged by the clinical team to be non-responders<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: yes; 1 (exacerbation of tic disorder)<br>Email correspondence with study authors: April 2014. We requested additional information from study authors but have not received a reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "Randomized" |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Unclear risk | "The clinical team was not blind to medication condition when making their recommendations. Therefore, as a reliability check of the clinical team's recommendations, one of the authors (J.W.) who was not involved in the clinical team meetings made independent recommendations based on the same data given to the clinical team. This rater was blind to drug condition except placebo" |
| Blinding of outcome assessment (detection bias) | Unclear risk | "The clinical team was not blind to medication condition when making their recommendations. Therefore, as a reliability check of the clinical team's recommendations, one of the authors (J.W.) who was not involved in the clinical team meetings made independent recommendations based on the same data given to the clinical team. This rater was blind to drug condition except placebo" |
| Incomplete outcome data (attrition bias) | Unclear risk | No information |
| Selective reporting (reporting bias) | Unclear risk | No protocol identified |
| Vested interest bias | High risk | Grants from the Shire Richwood Pharmaceutical Company and National Institute of Mental Health (Grants MH53554, MH45576 and MH50467) |

### *Pelham 2001a*

| Methods | Cross-over trial with 3 interventions<br>1. Concerta<br>2. Immediate-release methylphenidate<br>3. Placebo<br>Phases: 3 |
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| Participants | Number of participants screened: 70<br>Number of participants included: 68. Participants were randomly assigned to 1 possible drug condition order<br>Number of participants followed up: 68 (66 for ADHD symptoms)<br>Number of withdrawals: 2<br>Diagnosis of ADHD: DSM-IV (subtype not stated)<br>Age: mean 9.1 years (range 6 to 12)<br>IQ: mean 104.8<br>Sex: 89% boys, 11% girls<br>Methylphenidate naive: 0%<br>Ethnicity: Caucasian (94%), other (6%)<br>Country: USA<br>Setting: out-patient clinic (Summer Treatment Program)<br>Comorbidity: oppositional defiant disorder (43%), conduct disorder (37%)<br>Comedication: no<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Children 6 to 12 years of age with ADHD were recruited via several sources, including advertisement; physician, agency and school referral; and parent referral<br>2. All participants were required to be medicated with methylphenidate and to receive a stable dose for ≥ 4 weeks before the start of the study<br>**Exclusion criteria**<br>1. Medical condition that would contraindicate the use of stimulants<br>2. Physical condition or severe learning difficulty that would interfere with participation in study, including IQ < 80<br>3. Receiving additional medication for ADHD<br>4. Any medication with CNS effects, anticonvulsants or investigational medications<br>5. Reached menarche<br>6. Blood pressure at or above the 95th age and height percentile |
| Interventions | Participants were randomly assigned to different possible drug condition orders of immediate-release methylphenidate 3 times a day (t.i.d.); Concerta methylphenidate once a day (qd); and placebo<br>Mean methylphenidate dosage: 0.75 mg/kg (SD 0.34) (Three dosing levels were used: 5 mg immediate-release methylphenidate t.i.d./18 mg Concerta q.d.; 10 mg immediate-release methylphenidate t.i.d./36 mg Concerta q.d.; and 15 mg immediate-release methylphenidate t.i.d./54 mg Concerta q.d. The dose level used for each child was based on that child's methylphenidate dosing before the start of the study<br>Administration schedule: immediate-release methylphenidate 3 times a day; Concerta once daily<br>Duration of each medication condition: 7 days<br>Washout before study initiation: not described<br>Titration period: none<br>Treatment compliance: "virtually 100%" |

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| **Outcomes** | **ADHD symptoms**<br>1. Teachers and parents completed weekly symptom ratings using the IOWA Conners' Rating Scale<br>2. Teachers and parents rated oppositional defiant behaviour weekly using the Abbreviated Conners' Rating Scale<br>3. Teacher ratings on the Swanson, Kotkin, Agler, M-Flynn and Pelham Scale, daily<br>**Non-serious adverse events**<br>1. Reports of adverse events were collected via spontaneous reports over the course of the study. Additionally, each week, parents provided responses to questions on adverse events, sleep quality, appetite and tics |
| **Notes** | Sample calculation: no<br>Ethics approval: yes<br>**Comment from study authors**<br>1. All participants also received a behavioural intervention<br>**Key conclusion of study authors**<br>1. This investigation clearly supports the efficacy of the Concerta long-acting formulation of methylphenidate for parents who wish to have medication benefits for their child throughout the day and early evening<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; all participants were required to be medicated with methylphenidate and were receiving a stable dose for ≥ 4 weeks before the start of the study<br>Email correspondence with study author: June 2014. Emailed study author to ask for additional information but have not received a reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not described |
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Blinding of participants and personnel (performance bias) | Low risk | Referred to as double-blind; capsules were identical |
| Blinding of outcome assessment (detection bias) | Low risk | Referred to as double-blind; capsules were identical |
| Incomplete outcome data (attrition bias) | Unclear risk | Data reported for 66/70 for ADHD and behaviour |
| Selective reporting (reporting bias) | Unclear risk | No protocol available |
| Vested interest bias | High risk | Research was supported by ALZA Corporation, the manufacturers of Concerta<br>Conflicts of interest: Dr. Pelham is a member of the ALZA advisory committee on Concerta and its development. Drs. Hoffman and Lock are members of the ALZA paediatric advisory board |

*Pelham 2002*

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| **Methods** | Cross-over trial with 2 interventions<br>1. Methylphenidate<br>2. Placebo |

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| Participants | Number of participants screened: not stated<br>Number of participants included: 136 (all boys) (110 for 30-day follow-up). Participants were randomly assigned to 1 of 2 possible drug condition orders<br>Number of participants followed up: 136 (106 for 30-day follow-up)<br>Number of withdrawals: 0 (4 for 30-day follow-up)<br>Diagnosis of ADHD: DSM-III-R (therefore no subtype)<br>Age: mean 9.7 years (range 7.6 to 12.7)<br>IQ: mean 104.5<br>Methylphenidate naive: not stated<br>Ethnicity: Caucasian (81%), African American (15%)<br>Country: USA<br>Setting: Summer Treatment Program<br>Comorbidity: oppositional defiant disorder (53%), conduct disorder (24%)<br>Comedication: not stated<br>Sociodemographics: median family income: US $25,000, (range US $10,000 to > $100,000)<br>**Inclusion criterion**<br>1. Boys attending a psychiatric institute and clinic intensive Summer Treatment Program over 8 weeks<br>**Exclusion criteria**<br>1. Not stated |
| Interventions | Participants were randomly assigned to 1 possible drug condition order of 0.3 mg/kg methylphenidate and placebo<br>Mean methylphenidate dosage: 10 mg (SD 2.7)<br>Administration schedule: twice daily at 7:45 AM and 11:45 AM<br>Duration of each medication condition programme: 12 days (order randomly assigned daily over 6 weeks, doses administered over weekdays, except on Fridays); follow-up: 30 days<br>Washout before study initiation: 2 weeks medication free baseline in programme, unclear for follow-up<br>Titration period: none<br>Treatment compliance: not reported |
| Outcomes | **ADHD symptoms**<br>1. Programme: daily ratings of inattention/hyperactivity using IOWA Conners' Rating Scale completed by counsellor<br>2. Follow-up: daily ratings of inattention/hyperactivity using IOWA Conners' Rating Scale completed by teacher<br>**General behaviour**<br>1. Programme: daily ratings of oppositional defiant behaviour using IOWA Conners' Rating Scale completed by counsellor<br>2. Follow-up: daily ratings of oppositional defiant behaviour using IOWA Conners' Rating Scale, completed by teacher |

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| **Notes** | Sample calculation: no<br>Ethics approval: yes<br>**Comment from study authors**<br>1. Boys were told 50% of the time whether they were receiving placebo or medication and incorrectly 50% of the time; all boys received behavioural interventions over the course of the programme<br>**Key conclusion of study authors**<br>1. Expectancy (of treatment effectiveness) did not improve behaviour; only active medication improved behaviour<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: June 2014. Emailed study authors to ask for additional information but have not received a reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not described |
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Blinding of participants and personnel (performance bias) | Low risk | Capsules were identical |
| Blinding of outcome assessment (detection bias) | Low risk | Raters were blinded to medication condition |
| Incomplete outcome data (attrition bias) | Unclear risk | No loss to follow-up apparent during programme but data reported for 106/110 followed up in the community |
| Selective reporting (reporting bias) | Unclear risk | Although measures were rated daily, how data were aggregated/reported as a single result per phase is not clear |
| Vested interest bias | High risk | Supported by NIMH (Grant MH48157)<br>Conflicts of interest: Pelham served as an advisor for ALZA Corporation (see Pelham 2001a) |

### *Pelham 2005*

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| **Methods** | Eight-day, multi-centre, double-blind, randomised, dose-ranging, cross-over trial with 2 interventions<br>1. Methylphenidate transdermal system<br>2. Placebo<br>From a Summer Treatment Program |
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| Participants | Number of participants screened: 36<br>Number of participants included: 36 (33 boys, 3 girls). Participants were randomly assigned to 1 of 8 possible drug conditions<br>Number of participants followed up: 36<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-IV (subtype not stated)<br>Age: mean 9.6 years (range 6 to 13)<br>IQ: mean 105.3 (SD 18)<br>Stimulant-naive: 15 (42%)<br>Ethnicity: Caucasian (75%), African American (19%), Hispanic (3%), mixed African American/White (3%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: no; antidepressants were withdrawn from 2 participants before study enrolment<br>Sociodemographics: Parents were manual workers (6%), clerical/sales workers (32%), technicians/semi professionals (23%) and executives/major professionals (32%)<br>**Inclusion criteria**<br>1. Not stated<br>**Exclusion criteria**<br>1. Medical history prohibiting patients from taking stimulants or participating<br>2. Involvement in Summer Treatment Program activities<br>3. Skin problems or allergies to ingredients in the patches |
| Interventions | Participants were randomly assigned to 1 of 8 possible drug conditions of methylphenidate transdermal system and placebo<br>Methylphenidate transdermal system dosage: 6.25 cm² (0.45 mg/h), 12.5 cm² (0.9 mg/h), 25 cm² (1.8 mg/h)<br>Administration schedule: 1×/d (at 6:00 AM and 7:00 AM). Application sites were alternated each day between left and right hips<br>Duration of each medication condition (crossed with time of application): 1-day; patch worn for ≥ 12 hours/d<br>Duration of study: 8 days<br>Washout before study initiation: no<br>Medication-free period between interventions: no<br>Titration period: none<br>Treatment compliance: 100%. Parents returned patches and dosing records to the study site |
| Outcomes | **ADHD symptoms**<br>1. IOWA Conners' Rating Scale and Abbreviated Conners' Rating Scale were rated daily by parents, counsellors and teachers<br>**Non-serious adverse events**<br>1. Pittsburgh Side Effects Rating Scale completed daily by parents, counsellors and teachers<br>2. Any other adverse events that the child experienced were recorded<br>3. Skin irritation at application sites rated each day by parents for skin reactions or irritations before application, before removal and the following morning. Presence of erythema: none (0), very slight (1), well defined (2), moderate (3) or severe (4). Presence of discomfort: none (0), mild (1), moderate but tolerable (2) or severe (3) |

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| **Notes** | Sample calculation: yes (36 to 48)<br>Ethics approval: yes; institutional review board at each site approved the study<br>**Comments from study authors**<br>1. No children experienced a skin reaction severe enough that the study physician recommended discontinuing the patch<br>2. Limitations: short study duration, no controlled time-course evaluation<br>**Key conclusions of study authors**<br>1. Methyphenidate transdermal system produced significant effects that were similar to those previously reported with comparable methylphenidate doses<br>2. Substantial effect of application time on total daily functioning not apparent in this setting; additional controlled time-course studies will be necessary to fully evaluate the question of morning onset<br>3. Further study will be necessary to establish long-term efficacy and safety of the methylphenidate transdermal system<br>**Comment from review authors**<br>1. Families received monetary compensation to participate<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: no<br>Email correspondence with study authors: February to March 2014. We attempted to obtain supplemental information regarding randomisation, allocation concealment, washout period and efficacy and safety data from study authors but without success |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Study sponsor produced random orders and prepared medication kits in numbered containers for each participant |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | Treatment sequences were concealed until completion of the study |
| Blinding of outcome assessment (detection bias) | Low risk | Treatment sequences were concealed until completion of the study |
| Incomplete outcome data (attrition bias) | High risk | Evaluable participant data were analysed. As the result of record-keeping difficulties at 1 site, efficacy data were excluded for 5 participants<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Unclear risk | Not stated |
| Vested interest bias | High risk | Study was supported by Noven Pharmaceuticals. Furthermore, Dr. Pelham was supported by grants from NIAAA, NIDA, NIMH and NINDS<br>Conflicts of interest: Several study authors have received consulting fees and research funding and have been consultants and/or served on the Speakers' Bureaus of several pharmaceutical companies in the past year |

*Pelham 2011*

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| **Methods** | Three-week, randomised, double-blind, double-dummy, cross-over trial with 3 interventions<br>1. Immediate-release methylphenidate<br>2. Methylphenidate transdermal system<br>3. Placebo<br>Parents and children spent Friday evening to Sunday morning in a laboratory setting, where data collection took place |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 10 (all boys). Participants were randomly assigned to different drug orders of immediate-release methylphenidate, methylphenidate transdermal system and placebo<br>Number of participants followed up: 9<br>Number of withdrawals: 1<br>Diagnosis of ADHD: DSM-IV (combined (80%), hyperactive-impulsive (0%), inattentive (20%))<br>Age: mean 8.6 years (range 6.4 to 9.7)<br>IQ: mean 95.3 (range 83 to 109)<br>Methylphenidate naive: none; all receiving a stable dose of immediate-release methylphenidate before enrolment<br>Ethnicity: Caucasian (50%), African American (20%), Asian (0%), Hispanic (0%), Native American (10%), other (20%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder/conduct disorder (80%)<br>Comedication: no other psychotropics<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. ADHD diagnosis according to DSM-IV<br>2. IQ > 80<br>**Exclusion criteria**<br>1. Skin sensitivity or any significant dermatological disease<br>2. Atypical electrocardiogram results or hypertension<br>3. Atypical blood and urine test results or evidence of other medical condition that could be worsened by stimulant usage<br>4. Participants taking other psychotropics besides methylphenidate<br>5. Participants with psychopathology other than ADHD or oppositional defiant disorder or conduct disorder severe enough to merit additional treatment |

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| Interventions | Participants were randomly assigned to immediate-release methylphenidate, methylphenidate transdermal system or placebo<br>**Immediate-release methylphenidate**<br>Mean dosage: 30 mg/24 h<br>Administration schedule: 10 mg t.i.d. morning, lunch, afternoon<br>**Methylphenidate transdermal system**<br>Mean dosage: 33 mg/24 h<br>Administration schedule: two 10 cm² methylphenidate transdermal system patches worn for 24 hours at the buttock, with sides alternated daily<br>Time point: applied in the morning<br>Duration of each medication condition: 1 week<br>Washout before study initiation: 48 hours before study (no washout between treatment periods)<br>Titration period: none<br>Treatment compliance: Dosing and adhesion records were collected each week, but no data were available in the article |
| Outcomes | **ADHD symptoms**<br>1. Iowa Conners' Scale, rated by the laboratory classroom teacher at each treatment condition<br>**Non-serious adverse events**<br>1. Vital signs (temperature, weight, blood pressure, pulse) were measured Friday night by staff. Furthermore, vital signs were taken at 0, 4, 8 and 24 hours after the first dose on Saturdays<br>2. Adverse events were measured Friday night by staff and during weekdays by parents, and were reported spontaneously on Saturday evening and Sunday morning<br>3. Skin was examined Friday night by staff. Furthermore, nurses assessed each methylphenidate transdermal system application for skin irritation during the laboratory day before application and at 0.5, 12 and 24 hours after removal<br>4. Sleep: Parents rated the child's sleep during weekdays. On Friday and Saturday nights in the laboratory setting, nursing staff monitored children hourly between 9:00 PM and midnight and recorded sleep onset<br>5. Appetite: Parents rated this during weekdays |
| Notes | Sample calculation: no<br>Ethics approval: yes<br>**Key conclusion of study authors**<br>1. Methylphenidate transdermal system demonstrates efficacy and tolerability comparable with t.i.d. immediate-release methylphenidate<br>**Comments from study authors**<br>1. All participants had been receiving methylphenidate previously, and this may explain the small number of side effects<br>2. Furthermore, tolerability findings cannot be generalised to stimulant-naive children<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no; however, all participants had been receiving methylphenidate previously, and this may explain the small number of side effects<br>Email correspondence with study authors: July 2014. Emailed study authors to request additional information but have not received a reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Random assignment; no information about how |
| Allocation concealment (selection bias) | Low risk | Double-dummy procedure: All children received patches and capsules each day, with applicable placebos |
| Blinding of participants and personnel (performance bias) | Low risk | Double-blind |
| Blinding of outcome assessment (detection bias) | Low risk | Double-blind |
| Incomplete outcome data (attrition bias) | Low risk | One participant discontinued the study during the first week because of worsening behaviour while taking placebo and was not included in the analyses: all other participants completed the study<br>Adverse events: All participants receiving ≥ 1 dose of medication were included in the safety analysis<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Unclear risk | Not possible to find the protocol |
| Vested interest bias | High risk | Sponsored by a grant from Noven Pharmaceuticals (manufacturer of the MTS)<br>Conflicts of interest: Dr. Pelham has served as a consultant for Shire, McNeil, Noven, Celltech/Medeva, Novartis and Abbott Laboratories; has received honoraria from Shire and Janssen and research support from Shire, Alza, Eli Lilly, Noven and Cephalon; and holds common stock in Abbott Laboratories. Dr. Waxmonsky has served on the Speakers' Bureau for Novartis and has received research support from Eli Lilly and Shire Incorporated. Dr. Hoffman has served on the advisory board and Speakers' Bureau for Shire Pharmaceuticals and on the Speakers' Bureau for McNeil. Dr. Ballow has received research support from GlaxoSmithKline, Panacos, Boehringer Ingelheim, Pharmasset, Jacobus and Pharmena. Dr. Schentag has served as a consultant for or received support from Noven, Wyeth, Daiichi, Targanta Therapeutics and Astellas. Dr. Gonzalez is a full-time employee of P'Kinetics International Incorporated. No other conflicts of interest are known |

*Pelham 2014*

| Methods | Three-week, randomised, controlled, cross-over trial with 2 factors - medication and behavioural intervention - with daily medication changes<br>1. Methylphenidate<br>2. Placebo<br>3. Behavioural treatment |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 48 (44 boys, 4 girls). Participants were randomly assigned to 1 of 3 different doses of drug condition orders<br>Number of participants followed up: 47<br>Number of withdrawals: 1<br>Diagnosis of ADHD: DSM-VI (subtypes not stated)<br>Age: mean 9.35 years (range 5 to 12)<br>IQ: mean 106.33 (SD 14.61; range not stated)<br>Methylphenidate naive: not stated<br>Ethnicity: Caucasian (79%), African American (12.5%)<br>Country: USA<br>Setting: Summer Treatment Program<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. DSM-IV ADHD<br>2. IQ ≥ 80<br>3. No documented adverse response to, or medical conditions that would contraindicate use of, methylphenidate<br>**Exclusion criteria**<br>1. Not stated |
| Interventions | Participants were randomly assigned to 1 of 3 possible drug condition orders of 0.15 mg/kg/dose methylphenidate t.i.d.; 0.3 mg/kg/dose methylphenidate t.i.d.; 0.6 mg/kg/dose methylphenidate t.i.d. and placebo<br>Mean methylphenidate dosage: not clearly stated: "average doses were 5.4 mg (range = 2.5 – 10), 11 mg (range = 6.25 – 20), and 21 mg (range = 11.25 – 30), respectively"<br>Administration schedule: 3 time points<br>Duration of each medication condition: 0.15 mg dose for 4 days, 0.30 mg dose for 4 days and 0.6 mg dose for 3 days, switched daily<br>Washout before study initiation: not stated<br>Medication-free period between interventions: not stated<br>Titration period: not stated.<br>Treatment compliance: "One child's parents withdrew from the study after 2 days because of their concerns about possible side effects of the medication" |
| Outcomes | **ADHD symptoms**<br>1. IOWA Conners' Rating Scale: rated by counsellors, daily<br>**General behaviour**<br>1. IOWA Conners' Rating Scale O/D: rated by counsellors, daily<br>**Non-serious adverse events**<br>1. Counsellors completed the Pittsburgh Side Effects Rating Scale, daily<br>2. Study staff monitored ratings for clinically significant adverse events, daily |

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| **Notes** | Sample calculation: no<br>Ethics approval: yes<br>**Comments from study authors**<br>1. The prototypic child with ADHD could be treated with the equivalent of 0.15 mg/kg methylphenidate (5 mg per dose in the current sample) twice daily—a dose lower than that used in studies of stimulant treatment in the past 30 years—if he or she is receiving moderate- to high-intensity behavioural treatment<br>2. Our data show that stimulant doses can be reduced dramatically if a child is treated with behaviour modification<br>**Key conclusion of study authors**<br>1. "Results illustrate the importance of taking dosage/intensity into account when evaluating combined treatments; there were no benefits of combined treatments when the dosage of either treatment was high but combination of the low-dose treatments produced substantial incremental improvement over unimodal treatment"<br>**Comment from review authors**<br>1. Very difficult to understand the real effect of medication because of daily oscillation of the dose<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; only participants not having any documented adverse response to methylphenidate were included<br>Any withdrawals due to adverse events: yes (n = 1)<br>Email correspondence with study authors: April 2015. We emailed study authors to request supplemental information but have not received a response |

## Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomised |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | High risk | "The children, their parents, and clinical staff members were uninformed of medication condition and only the research coordinator, pharmacist and medical director had access to the medication order. The medical director could reveal medication conditions in cases of severe side-effect reports" |
| Blinding of outcome assessment (detection bias) | Low risk | "Observers were independent staff members who were not involved in the children's treatment" |
| Incomplete outcome data (attrition bias) | Unclear risk | Not stated<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Unclear risk | No access to protocol. No description in clinicaltrials.gov |
| Vested interest bias | Low risk | Funded by a grant from the National Institute of Mental Health (MH62946). Dr. Pelham was funded by grants from the National Institutes of Health (MH62946, MH69614, MH53554, MH69434, MH65899, MH78051, MH062946, NS39087, AA11873, DA12414, HD42080) and the Institute of Education Sciences (L03000665A). Dr. Fabiano was supported in part by a Ruth S. Kirschstein National Research Service Award Predoctoral Fellowship (1F31MH064243-01A1) and by the Department of Education, Institute of Education Sciences (R324J06024, R324B06045)<br>Conflicts of interest: not declared |

*Perez-Alvarez 2009*

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| **Methods** | Twelve-month, randomised, controlled, parallel study with 2 different treatment strategies<br>A) Participants with a score ≧ 2.5/1.8 on the Swanson, Nolan and Pelham Scale, Fourth Edition (teacher/parents), were randomly assigned to<br>1. Concerta<br>2. Humanistic psychology<br>3. Concerta + psychology<br>B) Participants with score < 2.5/1.8 on the Swanson, Nolan and Pelham Scale, Fourth Edition, were randomly assigned to<br>1. Humanistic psychology<br>2. Concerta + psychology |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 150<br>Number randomly assigned: Concerta + psychology 59, humanistic psychology 59<br>Number followed up: Concerta + psychology 59, humanistic psychology 59<br>Number of withdrawals: Concerta + psychology 0, humanistic psychology 0<br>Diagnosis of ADHD: DSM-IV-TR (combined (67%), hyperactive-impulsive (0%), inattentive 33%))<br>Age: mean 10 years (range 7 to 14)<br>Sex: boy:girl 4:1 for those with combined type; 1:3 for those with inattentive type<br>Methylphenidate naive: 100%<br>Ethnicity: not stated<br>Country: Spain<br>Setting: out-patient clinic<br>Comorbidity: no<br>Comedication: no<br>IQ: > 70<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. ADHD DSM-IV-TR, combined or inattentive type<br>2. 7 to 15 years<br>3. IQ > 70<br>**Exclusion criteria**<br>1. Previous medication or therapy<br>2. Comorbidity |
| **Interventions** | Participants were randomly assigned to Concerta + psychology or humanistic psychology<br>OROS methylphenidate dose: not stated<br>Administration schedule: not stated<br>Duration of intervention: 12 months<br>Titration period: not stated<br>Treatment compliance: not stated |
| **Outcomes** | **ADHD symptoms**<br>1. Swanons, Nolan and Pelham, Fourth Edition (18-item): rated at baseline, 6 months and 12 months by teachers and parents |

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| **Notes** | Sample calculation: no<br>Ethics approval: yes<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: no<br>**Key conclusion of study authors**<br>1. In summary, while further confirmation is awaited, the cognitive PASS assessment may be a useful tool for better diagnostic and prognostic classification in comparison with behavioural phenotyping<br>**Comment from review authors**<br>1. In study methods and data extraction, all participants receiving Concerta + psychology (3A + 2B) were analysed together, as were all participants receiving humanistic psychology (2A + 1B)<br>Email correspondence with study authors: June 2014. We received supplemental information regarding funding, ethics approval and protocol from the study authors, although they were not able to send data from the Swanson, Nolan and Pelham Scale, Fourth Edition |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Participants were randomly assigned, but no information was given to explain how assignment was done |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | High risk | No blinding |
| Blinding of outcome assessment (detection bias) | High risk | No blinding |
| Incomplete outcome data (attrition bias) | Low risk | No drop-outs<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Unclear risk | No; all planned analyses are described in the paper |
| Vested interest bias | Low risk | Study was not funded. Research was part of the workday, participants were voluntary and no funding was needed to implement the study<br>Conflicts of interest: none. Investigators are staff members at institutions (affiliations) reported in the paper |

*Pliszka 1990*

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| **Methods** | Four-week, double-blind, cross-over trial, in which children were randomly assigned to the following<br>1. Two doses of methylphenidate (low: 0.25 mg/kg to 0.40 mg/kg; and high: 0.45 mg/kg to 0.70 mg/kg)<br>2. Placebo |

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| Participants | Number of participants screened: 79<br>Number of participants included: 46<br>Number of participants followed up: 43 (30 without anxiety, 13 with anxiety)<br>Number of withdrawals: 3. Participants were randomly assigned to different orders of methylphenidate low dose, methylphenidate high dose or placebo<br>Diagnosis of ADHD: DSM-III (subtype not stated)<br>Age: mean 9 years (range not reported)<br>IQ: > 70<br>Sex: not stated<br>Methylphenidate naive: not stated<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: anxiety (30%), oppositional defiant disorder (56.0%), conduct disorder (23.3%) (Participants who expressed transient anxiety or depression about consequences of punishment for misbehaviour were considered to not meet the criteria for an overanxious disorder)<br>Comedication: no<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. DSM-III-R criteria for ADHD<br>2. Candidate for a stimulant trial<br>**Exclusion criteria**<br>1. None stated<br>No patients met the criteria for any psychotic or depressive disorder. Participants were free of medication, as well as any other medical disorder |
| Interventions | A total of 4 weeks of medication. First week always placebo; remaining 3 weeks, participant were randomly assigned to different orders of placebo and low- (0.25 mg/kg to 0.40 mg/kg) and high-dose (0.45 mg/kg to 0.70 mg/kg) methylphenidate. Doses were as follows: 5 mg and 10 mg for weight < 25 kg; for those overweight, the 2 dose conditions were 10 mg and 20 mg<br>Administration schedule: b.i.d., 7:00 AM and 12 noon. Saturday, the dose was adjusted so that it was given 90 minutes before measurements were taken<br>Duration of each medication condition: 1 week<br>Washout before study initiation: not relevant; did not take methylphenidate before<br>Medication-free period between interventions: 17 hours<br>Titration period: none<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. IOWA Conners' Teacher Rating Scale (both Inattention/Overactivity and Aggressive subscales): rated weekly by teachers at the end of each week |

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| Notes | Sample calculation: no information<br><br>Ethics approval: no information<br><br>**Comments from study authors**<br><br>1. Data strongly suggest that children who met criteria for ADHD and anxiety are not children who simply have become "demoralised" by frequent conflicts with parents and teachers. They represent a distinct subgroup<br>2. It is unclear from these data whether children with comorbid ADHD and anxiety form a separate subtype of ADHD, similar to the DSM-III diagnosis of ADD without hyperactivity, or whether this is a group of children with primary anxiety that may lead to oppositional behaviour and temper tantrums, and the presence of these symptoms may lead parents and teachers to report inattention and overactivity when the symptoms may not be objectively present<br>3. This study strongly suggests that it is important to control for the presence of anxiety disorders in research on ADHD<br>4. Analyses were made on the basis of whether anxiety was present with ADHD. To meet criteria for anxiety, children had to report the symptoms themselves<br><br>**Key conclusions of study authors**<br><br>1. A total of 43 participants completed a double-blind trial of methylphenidate; participants with comorbid anxiety had a significantly poorer response<br>2. Results suggest that ADHD with comorbid anxiety may characterise children with primary anxiety who develop secondary inattentiveness, or may represent a different subtype of ADHD, perhaps similar to the condition of attention deficit disorder without hyperactivity, as under DSM-III<br>3. ADHD participants with anxiety were rated significantly lower on the IOWA Conners' Teacher Rating Scale, Inattention/Overactivity subscale, than those without anxiety, although the mean score for both groups was well into the disturbed range<br><br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br><br>Email correspondence with study authors: November 2013. We received from the study authors supplemental information regarding participants' intellectual function and funding and additional data. The raw data no longer exist; therefore we cannot analyse data from different periods in the cross-over trial, only endpoint data |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomly assigned to placebo and low-dose and high-dose methylphenidate |
| Allocation concealment (selection bias) | Unclear risk | Randomly assigned to placebo and low-dose and high-dose methylphenidate. Not stated how investigators allocated participants to the intervention |
| Blinding of participants and personnel (performance bias) | Low risk | The child, his or her parents, teachers and research assistants were all blinded to drug status |
| Blinding of outcome assessment (detection bias) | Low risk | The child, his or her parents, teachers and research assistants were all blinded to drug status |
| Incomplete outcome data (attrition bias) | Unclear risk | Only 3 drop-outs. All other participants were included in the final analysis<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Low risk | The entire outcome as stated in the methods was reported in the results |
| Vested interest bias | Low risk | National Institute of Mental Health (NIMH)<br>Conflicts of interest: not declared |

*Pliszka 2000*

| Methods | Three-week, randomised, double-blind, placebo-controlled, parallel trial with 3 arms<br>1. Adderall<br>2. Methylphenidate<br>3. Placebo |
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| Participants | Number of participants screened: 73<br>Number of participants included: 58<br>Number randomly assigned: methylphenidate 20, placebo 18<br>Number followed up: methylphenidate 19, placebo 16<br>Number of withdrawals: methylphenidate 1, placebo 2<br>Diagnosis of ADHD: DSM-IV. Diagnostic Interview Schedule for Children diagnosis of ADHD (subtype not stated)<br>Age: mean 9 years (range not reported)<br>IQ: > 75<br>Sex: not stated<br>Methylphenidate naive: methylphenidate 5 (25%), placebo 1 (6%)<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder (methylphenidate 14%, placebo 10%), conduct disorder (methylphenidate 1%, placebo 2%), anxiety disorder (methylphenidate 20%, placebo 5%)<br>Comedication: not stated<br>Sociodemographics: not stated. No significant difference in baseline demographics were noted between the 2 groups<br>**Inclusion criteria**<br>1. Children in grades 1 to 5<br>2. ADHD according to Diagnostic Interview Schedule for Children<br>3. IQ > 75<br>4. ≥ 1.5 SD above the mean for his/her age and sex on the IOWA Conners' Teacher Rating Scale, Inattention/Overactivity factor<br>**Exclusion criteria**<br>1. Other medical illness<br>2. Meeting Diagnostic Interview Schedule for Children criteria for major depression episode, manic episode or tic disorder<br>3. History of psychosis or signs of psychosis or significantly depressed mood on the mental status examination<br>4. Current treatment consists of non-stimulant psychotropic medication |
| Interventions | Participants were randomly assigned to immediate-release methylphenidate or placebo<br>Mean methylphenidate dosage: total dose 25.2 mg/d<br>Administration schedule: 17 (85%) received 2 or more doses<br>Time points: 1 to 3 times a day: morning, after school and additional noon if needed<br>Duration of intervention: 3 weeks<br>Titration period: none<br>Treatment compliance: not stated. Dosage was adjusted at the end of weeks 1 and 2 via an algorithm based on teacher and parent ratings |
| Outcomes | **ADHD symptoms**<br>1. IOWA Conners' Teacher Rating Scale: rated twice daily (morning and afternoon) Mondays through Thursdays<br>**General behaviour**<br>1. Conners' Global Index: parent-rated<br>**Non-serious adverse events**<br>1. Multi-Modality Treatment of ADHD (MTA) side effects scale: parent-rated weekly (Thursday evenings) |

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| **Notes** | Sample calculation: no<br>Ethics approval: no<br>**Comment from study authors**<br>1. Mean mg/kg dose for methylphenidate non-responders was 0.43, which is less than the 0.3 mg/kg to 0.8 mg/kg dose known to be required for adequate response in some children with ADHD<br>**Key conclusion of study authors**<br>1. Both medications were superior to placebo for reducing inattentive and oppositional symptoms in the classroom and on the Conners' Global Index<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: January 2014. Supplemental information received from study authors |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomly assigned: "We used a random number generator to determine which of the 3 groups the child was assigned to" |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | Parents, children, teachers and treating physicians were blind to medication status. Medication was crushed, mixed with a blue food powder and placed in opaque capsules |
| Blinding of outcome assessment (detection bias) | Low risk | Placebo participants were randomly assigned to follow methylphenidate or Adderall treatment algorithm. The blinded psychiatrist could not determine the child's medication status simply by knowing which algorithm was being followed. Principal Investigator knew the medication status of participants |
| Incomplete outcome data (attrition bias) | High risk | Morning and afternoon IOWA scores were averaged at the end of the week<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Low risk | All planned outcomes were reported |
| Vested interest bias | High risk | Research funded by Shire Richwood Incorporated<br>Conflicts of interest: Dr. Browne is currently with Watson Pharmaceuticals, Corona, California |

### *Pliszka 2007*

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| **Methods** | Five-week double-blind, cross-over, placebo-controlled trial, conducted to examine electrophysiological effects of methylphenidate on inhibitory control in children with ADHD<br>1. Methylphenidate<br>2. Placebo |

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| Participants | Number of participants screened: 12<br>Number of participants included: 12 (8 boys, 4 girls). Participants were randomly assigned to 1 of (not stated) possible drug condition orders<br>Number of participants followed up: 12<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-IV (combined (100%))<br>Age: mean 12.3 years (range 9 to 15)<br>IQ: not stated<br>Methylphenidate naive: 10<br>Ethnicity: Caucasian (67%), African American (8%), Hispanic (25%)<br>Country: USA<br>Setting: not stated<br>Comorbidity: oppositional defiant disorder (45%)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. ADHD, combined type<br>2. Conners' Global Index: restless/impulsive ratings ≥ 1.5 SD above the mean for child's age and sex on both parent and teacher ratings<br>**Exclusion criteria**<br>1. General Cognitive Ability on DIfferential Abilities Scale > 85<br>2. Any substance abuse/dependence<br>3. Any neurological disease<br>4. Long-term use of any medicine<br>5. Learning disability |
| Interventions | Participants were randomly assigned to different possible drug condition orders of 5 mg, 10 mg, 15 mg, 20 mg methylphenidate and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: 3 time points<br>Duration of each medication condition: 7 days<br>Washout before study initiation: not stated<br>Medication-free period between interventions: 0<br>Titration period: none initiated before/after randomisation |
| Outcomes | **General behaviour**<br>1. Parents and Teacher Conners' Global Index (CGI) |

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| Notes | Sample calculation: no<br>Ethics approval: yes; study approved by the Institutional Review Board of the University<br>**Comments from study authors**<br>1. Several limitations of the study should be noted<br>2. Our sample was relatively small and was composed entirely of children with ADHD, combined type alone, and no other significant comorbidity other than oppositional defiant disorder<br>3. All participants were positive responders to methylphenidate<br>4. Our sample was too small to examine for effects of sex and ethnicity, and results should be replicated in a larger sample<br>**Key conclusions of study authors**<br>1. Methylphenidate may improve inhibitory control by enhancing brain mechanisms that trigger the inhibitory process and make stopping a motor act more probable (reflected by increased N200) and by increasing attentional resources to the task when unsuccessful inhibitions occur (as reflected by increased NoGo-P3)<br>2. These results are consistent with functional imaging studies, suggesting a role for the right frontal inferior cortex and the cingulate cortex in the pathophysiology of ADHD<br>**Comment from review authors**<br>1. Although this study includes only good responders to methylphenidate, this occurred by chance and not by design, as 10 out of 12 were treatment naive<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: May 2014. Study authors could not give us the necessary data (e.g. separate data for each intervention period); therefore we could not use Conners' Global Index data |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "Double-blind, crossover, placebo-controlled" |
| Allocation concealment (selection bias) | Low risk | From email: One investigator was assigned on the basis of chance; the other remained blinded |
| Blinding of participants and personnel (performance bias) | Unclear risk | Double-blind. One investigator assigned on the basis of chance; the other remained blinded |
| Blinding of outcome assessment (detection bias) | Low risk | One investigator assigned on the basis of chance; the other remained blinded |
| Incomplete outcome data (attrition bias) | Low risk | No drop-outs<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | No protocol identified |
| Vested interest bias | Low risk | Funded by the National Institute of Mental Health Grant R01 MH63986<br>Conflicts of interest: Pliszka received honoraria and research support from Shire and MacNeil and research support from Ely Lilly and Cephalon |

*Quinn 2004*

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| **Methods** | Cross-over trial with 3 interventions<br>1. Dex,l-methylphenidate<br>2. Dexmethylphenidate<br>3. Placebo |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 32. Participants were randomly assigned to possible drug condition orders<br>Number of participants followed up: 31 (all boys)<br>Number of withdrawals: 1<br>Diagnosis of ADHD: DSM-IV (combined (87.1%), hyperactive-impulsive (9.7%), inattentive (3.2%))<br>Age: not stated (range 9 to 12 years)<br>IQ: > 80<br>Methylphenidate naive: 0%<br>Ethnicity: not stated<br>Country: USA and Canada<br>Setting: out-patient clinic<br>Comorbidity: (0%)<br>Comedication: 0% for other medications for ADHD<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Male, between 9 and 12 years of age<br>2. Meet DSM-IV criteria for ADHD, as confirmed by the Diagnostic Interview Schedule for Children<br>3. Clinical history of positive response to treatment with ≥ 20 mg/d of dex,l-MPH for ≥ 1 month<br>4. Rating > 90th percentile on Parent and Teacher Versions of the Swanson, Nolan and Pelham ADHD Rating Scale<br>5. IQ ≥ 80 as assessed by a validated intelligence test<br>**Exclusion criteria**<br>1. Any associated CNS, cardiovascular, renal or respiratory disorder<br>2. Known sensitivity to methylphenidate or receiving other medication for ADHD<br>3. Comorbid clinical disorders reported during clinical interview or identified during administration of the Diagnostic Interview Schedule for Children |
| **Interventions** | Participants were randomly assigned to 1 of the possible drug condition orders of dex,MPH, dex,l-MPH and placebo. Both the order of drugs and the dose sequence were randomly assigned<br>Mean methylphenidate dosage: d-MPH 2.5 mg, 5 mg or 10 mg; dex,l-MPH 5 mg, 10 mg or 20 mg<br>Administration schedule: once at 8.30 AM<br>Duration of each medication condition: 1 day. Interventions were separated by ≥ 6 days<br>Washout before study initiation: 24 hours<br>Medication-free period between interventions: ≥ 24 hours<br>Titration period: none<br>Treatment compliance: administered at the laboratory |

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| Outcomes | **ADHD symptoms**<br>1. Conners, Loney and Milich (CLAM) Scale: teacher-rated, at 2 hours, 3.5 hours and 6 hours (CLAM aggressive/defiant, CLAM inattention/overactivity)<br>2. Conners' Hyperactivity Index: teacher-rated, at 2 hours, 3.5 hours and 6 hours<br>**Non-serious adverse events**<br>1. Adverse events<br>2. Average pulse rate also measured |
| Notes | Sample calculation: no<br>Ethics approval: approved by each centre's institutional review board<br>**Comments from study authors (limitations)**<br>1. Study was conducted in a laboratory school setting (no healthy participants, high level of staffing, short and repetitive classroom period compared with a regular classroom setting)<br>2. Relatively small sample size<br>3. Narrow age range<br>**Key conclusions of study authors**<br>1. Efficacy of methylphenidate resides in the d-isomer. Elimination of the i-isomer does not diminish the efficacy of an acute dose of methylphenidate<br>2. This study demonstrates that single low (2.5 mg), medium (5 mg) and high (10 mg) doses of dexmethylphenidate match the efficacy of equimolar single low (5 mg), medium (10 mg) and high (20 mg) doses of dex,l-methylphenidate over a 6-hour period, based on repeated measurements of a surrogate measure of academic performance<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; included only children stable on methylphenidate<br>Email correspondence with study authors: July to August 2014. We contacted study authors to obtain safety data and supplemental information regarding randomisation, allocation concealment, blinding, handling of incomplete outcome data and outcomes, but we were not successful |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomised. Both the order of drugs and the dose sequence were randomly assigned |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | Except for first practice day, on which only participants were blinded, administration of doses was double-blinded throughout the study |
| Blinding of outcome assessment (detection bias) | Unclear risk | Double-blind. Blinded observers rated behaviour |
| Incomplete outcome data (attrition bias) | Unclear risk | Study authors report only 1 respondent (LTFU), not related to side effects<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Unclear risk | All outcomes reported. No protocol available |
| Vested interest bias | High risk | Study was funded by Celgene<br>Conflicts of interest: All study authors disclosed that they have past and present affiliations with the pharmaceutical industry |

*Ramtvedt 2013*

| Methods | Six-week, cross-over trial with 3 interventions<br>1. Methylphenidate<br>2. Placebo<br>3. Dextroamphetamine<br>Phases: 3 |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 36. Participants were randomly assigned to 1 of 6 possible drug condition orders<br>Number of participants followed up: 36 (29 boys, 7 girls) (n = 34 for adverse event data)<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-IV-TR (combined (69%), hyperactive-impulsive (3%), inattentive (28%))<br>Age: mean 11.4 years (range 9 to 14)<br>IQ: mean 90.9<br>Methylphenidate naive: 100%<br>Ethnicity: not stated<br>Country: Norway<br>Setting: out-patient clinic<br>Comorbidity: anxiety/depressive disorder (n = 9, 25%), oppositional defiant disorder (n = 20, 55%), learning disability (n = 22, 61%) and Asperger syndrome (n = 1, 3%)<br>Comedication: no<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. ADHD diagnosis rated as > 2 SD above the mean on the Conners' Rating Scale, DSM-IV Inattention and/or DSM-IV Hyperactivity-Impulsivity subscales<br>2. Between 9 and 14 years of age<br>3. No prior treatment with stimulants<br>4. Stimulant treatment that has been approved by a paediatrician or psychiatrist<br>**Exclusion criteria**<br>1. Moderate to severe mental retardation<br>2. Psychosis<br>3. Brain injury<br>4. Sensory deficits, motor impairment or both<br>5. Epilepsy<br>6. Factors that would substantially reduce the possibility of obtaining reliable observations from a parent or teacher |
| Interventions | Participants were randomly assigned to 1 of 6 possible drug condition orders of methylphenidate (30 mg/d to 40 mg/d), dextroamphetamine (10 mg/d to 20 mg/d) and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: methylphenidate, 3 time points (morning, lunch and afternoon); dextroamphetamine, 2 time points (morning and afternoon)<br>Duration of each medication condition: 2 weeks (first week: low dose (30 mg/d), second week: high dose (40 mg/d))<br>Washout before study initiation: no; all were stimulant-naive<br>Medication-free period between interventions: yes; Saturday and Sunday (48 hours)<br>Titration period: 2 weeks initiated after randomisation<br>Treatment compliance: not stated |

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| Outcomes | **ADHD symptoms**<br>1. DSM-IV Inattention and Hyperactive-Impulsive subscales from Conners' Rating Scale – Revised, Long Version, Parent and Teacher Forms<br>2. 21-item ADHD questionnaire was developed for this study (8 items reflecting inattention, 6 items reflecting hyperactive-impulsive behaviour and 4 items reflecting oppositional defiant behaviour), completed daily from Monday to Friday, every week by parents and teachers (Ramtvedt 2013)<br>3. Children's self-report scale - developed for this study: 8 items, rated weekly by the children themselves<br>**General behaviour**<br>1. Child Behavior Checklist<br>2. Teacher Rating Form<br>3. ADHD questionnaire - Inattentive subscale, teacher-rated<br>**Non-serious adverse events**<br>1. Barkley Side Effect Rating Scale: Parents were instructed to rate side effects in co-operation with their child at the end of each week during the trial |
| Notes | Sample calculation: not stated<br>Ethics approval: yes<br>**Comments from study authors**<br>1. Drugs were not camouflaged in identical capsules, increasing the risk for identification of drug order<br>2. In only 1 case, a parent identified the drug order with certainty. That particular child was removed from the study<br>3. ADHD questionnaire, used to rate ADHD symptoms during the stimulant trial, was developed for this study and cannot be considered equivalent to well-established ADHD Rating Scales<br>4. Sample size might not have been sufficient to detect subtle differences between stimulants at the group level<br>**Key conclusions of study authors**<br>1. Methylphenidate and dextroamphetamine were significantly effective. No significant superiority of 1 stimulant over the other was detected at the group level<br>2. Adverse events associated with dextroamphetamine vs methylphenidate appear similar at the group level but may differ substantially in individual children<br>3. Overall, insomnia and decreased appetite were significantly associated with stimulants<br>**Comments from review authors**<br>1. This does not seem to be a particularly useful paper because the main point (not explicitly stated) was to obtain an equivalence for the QbTest (measures the 3 core signs of ADHD). As a result of this, the medication regimen was dedicated to find the best effects of both medications<br>2. Study authors stated that the primary outcome measure was developed for the study and cannot be considered equivalent to known ADHD Rating Scales. Therefore, we have not used the data on ADHD symptoms in our analyses<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: no<br>Email correspondence with study authors: April 2015. We obtained supplemental information or data regarding comedication, randomisation and blinding |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Participants were randomly and evenly assigned to each of 6 possible drug orders. "The children were assigned to the six possible drug condition orders by drawing numbers" |
| Allocation concealment (selection bias) | Unclear risk | Not clear |
| Blinding of participants and personnel (performance bias) | High risk | Participants, parents, teachers and test administrators were blinded to drug order. One parent identified the drug order. Tablets of similar colours, shapes and textures were administered, but the drugs were not camouflaged in identical capsules |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not stated |
| Incomplete outcome data (attrition bias) | Unclear risk | Not stated |
| Selective reporting (reporting bias) | Unclear risk | No access to protocol |
| Vested interest bias | High risk | First phase was conducted as part of ordinary clinical practice at Neuropsychiatric Unit, Østfold Hospital Trust. Second and third phases, data analysis and preparation of manuscript were sponsored by South-Eastern Norway Regional Health Authority, and also by Østfold Hospital Trust and National Resource Centre for ADHD, both under the umbrella of South-Eastern Norway Regional Health Authority<br>Conflicts of interest: Henning Aabech is a member of the Strattera Advisory Board, Eli Lilly Norway |

*Rapport 1985*

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| Methods | Triple-blind, randomised, cross-over trial with 4 interventions<br>1. Placebo<br>2. 5 mg methylphenidate<br>3. 10 mg methylphenidate<br>4. 15 mg methylphenidate<br>**Phases**<br>1. Week 1: baseline assessment<br>2. Weeks 2 to 5: cross-over trial |

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| Participants | Number of participants screened: 22<br>Number of participants included: 14 (12 boys, 2 girls)<br>Number of participants followed up: 11<br>Number of withdrawals: 1<br>Number of participants excluded during the study: 2<br>Diagnosis of ADHD: DSM-III (subtype not stated)<br>Age: 8.3/7.75 years (range 6 to 10)<br>IQ: > 100<br>Methylphenidate naive: not stated<br>Ethnicity: Caucasian (86%), not stated (14%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: no<br>Sociodemographics: Low to middle socioeconomic status<br>**Inclusion criteria**<br>1. DSM-III diagnosis of ADHD by the child's paediatrician and the clinic's directing clinical psychologist<br>2. Maternal report of a developmental history consistent with ADD-H (Barkley 1981)<br>3. Maternal rating of ≥ 2 SD above the mean for the child's age on the Werry-Weiss-Peters Activity Scale<br>4. Teacher rating > 15 on the Abbreviated Conners' Teacher Rating Scale<br>5. Children showing a favourable response to methylphenidate (≥ 25% mean increase in classroom on-task behaviour and decrease ≥ 2 SD on the Abbreviated Conners' Teacher Rating Scale (compared with baseline levels) during any of the active medication weeks)<br>6. Performance on the Matching Familiar Figures Test characteristic of a "fast-inaccurate or impulsive" responder (i.e. faster than average responses and higher than average error rates for the child`s age)<br>**Exclusion criteria**<br>1. Any gross neurological, sensory or motor impairment<br>2. Those currently taking medication<br>3. Those classified as non-responders, defined as neither improved (methylphenidate-induced facilitation ≥ 25%) on the Paired Associates Learning test nor declined in relation to baseline and placebo |
| Interventions | Participants were randomly assigned to 1 of 24 possible drug condition orders of fixed doses of methylphenidate (5 mg, 10 mg, 15 mg) and placebo. As a result of the small sample size, not all drug orders were used. Post hoc comparison showed that doses were distributed approximately equally across different positions in the sequence<br>Administration schedule: once daily, in the morning<br>Duration of each medication condition: 7 days<br>Washout before study initiation: none, but all weekly dosage changes occurred on Saturdays to control for potential rebound effects<br>Titration period: none<br>Treatment compliance: Both used and unused envelopes with capsules were returned to control for medication compliance. No results regarding compliance were reported |
| Outcomes | **ADHD symptoms**<br>1. Abbreviated Conners; Teacher Rating Scale: Teacher rated symptoms each Friday, in the morning, or at the end of each treatment condition<br>2. Dosage changes occurred on Saturdays<br>No useable data |

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| **Notes** | Sample calculation: not stated<br>Ethics approval: not stated<br>**Key conclusion of study authors**<br>1. Results of the present investigation demonstrate a functional relationship between psychoactive medication and impulsivity, attention and behaviour of children with ADD in classroom settings<br>**Comment from review authors**<br>1. Although study authors refer in 1 of the articles to the other 2 articles as a recent study and a past investigation, it seems to us that these articles discuss the exact same study<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; included only methylphenidate-favourable responders<br>Any withdrawals due to adverse events: *n*o<br>Email correspondence with study authors: July 2013. Study authors informed us that original records were shredded after 20 years, and that they could not provide the requested data ( Ramstad 2013c [pers comm] ) |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Order of drug administration was determined by randomly assigning each child to 1 of 24 possible drug disorders |
| Allocation concealment (selection bias) | Low risk | Methylphenidate was packaged by the pharmacist in coloured gelatin capsules to avoid detection of dose and taste. Capsules were placed in individually dated envelopes to ensure accurate dose administration |
| Blinding of participants and personnel (performance bias) | Low risk | Triple-blind design |
| Blinding of outcome assessment (detection bias) | Low risk | Teachers and observers were blind to when medication was administered and what specific doses were given |
| Incomplete outcome data (attrition bias) | High risk | Data from 2 of 12 children in the present investigation were not included in the statistical analyses because they were classified as non-responders according to results of the Paired Associates Learning test |
| Selective reporting (reporting bias) | Unclear risk | Not possible to receive a copy of the protocol |
| Vested interest bias | Unclear risk | No information regarding funding<br>Conflicts of interest: not declared |

### *Rapport 1987*

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| **Methods** | Double-blind, placebo-controlled, cross-over trial with 2 interventions<br>1. Methylphenidate (5 doses)<br>2. Placebo<br>Phases: Five methylphenidate doses were given in a randomly assigned, counterbalanced sequence. Children received each dose for 6 consecutive days |

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| Participants | Number of participants screened: 134. Children were screened for inclusion after referrals from paediatricians, psychiatrists and school personnel over a 5-year period. Different publications reported different numbers of included children, ranging from 22 to 76 children. Study authors stated: "this is a sample of children who were recruited across several years with publications presenting findings over that time period. Thus, there were slight differences in sample composition as more participants were added. But essentially these studies included the same sample". Participants were randomly assigned to 1 of 4 possible drug condition orders. Different publications reported different figures for missing data, number of withdrawals and other important information. This was included in our 'Risk of bias' assessment and is reported in the 'Risk of bias' table. One-day washout (Saturdays) was described in each publication<br><br>Age: 10 to 12 years. Reported ages varied across publications but, in most publications, ranged from 6 to 11 years<br><br>DSM-III diagnosis of ADHD (subtype not stated)<br><br>IQ: mean 101. DuPaul 1993 stated that children were of average or above average intelligence<br><br>Sex: 37 boys and 5 girls (Rapport 1987)<br><br>Methylphenidate naive: 100% (in both Rapport 1987 + DuPaul 1993). In Rapport 1987, 8 had experienced brief trials of stimulants within the previous 4 years<br><br>Ethnicity: not stated<br><br>Country: USA<br><br>Setting: out-patient clinic<br><br>Comorbidity: not stated<br><br>Comedication: No children were taking medication before participating in the study (DuPaul 1993 in Rapport 1987)<br><br>Sociodemographics: low to middle socioeconomic status (Hollingshead) (Rapport 1987 and DuPaul 1993 in Rapport 1987)<br><br>**Inclusion criteria**<br><br>1. Independent diagnosis by the child's paediatrician and the Rhode Island Construction Leadership Council (CLC), directing clinical psychologists using DSM-III criteria for ADHD<br>2. Maternal report of a developmental history consistent with ADHD and problems in ≥ 50% of situations on the Home Situations Questionnaire<br>3. Maternal rating ≥ 2 SD above the mean for the child's age on the Werry-Weis-Peters Activity Scale<br>4. Teacher rating on the Abbreviated Conners' Teacher Rating Scale > 15 - the designated cutoff score for hyperactivity<br>5. Performance on the Matching Familiar Figures Test characteristic of a "fast inaccurate or impulsive" responder (i.e. faster than average responses and higher than average error rates for the child's age)<br>6. Absence of any gross neurological, sensory or motor impairment as determined by paediatric examination<br><br>We believe that this study consists of 13 articles. When study authors were asked about that, Dr. DuPaul answered that many of the publications based on the Rhode Island Construction Leadership Council (CLC) Clinic "were fairly the same study". Even though some publications describe 6 inclusion criteria and others describe 5, we believe that the publications are based on the same study (Ramstad 2013b [pers comm]) |

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| Interventions | Participants were randomly assigned to 1 of 5 possible drug condition orders of methylphenidate and placebo. Methylphenidate was described by each child's paediatrician in the following doses: placebo, 5 mg, 10 mg, 15 mg and 20 mg. Fixed doses were prescribed (rather than mg/kg)<br><br>Administration schedule: Children were seen once a week at the Rhode Island Construction Leadership Council (CLC) Clinic. Baseline measures were obtained during the child's second clinic visit to allow familiarisation with clinic personnel and testing procedures. On subsequent testing days, children were administered a capsule of the active agent (methylphenidate) or placebo. This procedure continued until each child received each dose for 6 consecutive days. All weekly dosage changes occurred on Sundays, and no medication was administrated on Saturdays, to allow for needed washout due to inter-individual variation in serum and blood plasma levels following acute administration of methylphenidate. All children described in the present study were classified as favourable responders, whereas those whose performance did not improve to this extent were classified as non-responders. These criteria were established a priori. All children described in the present study were favourable responders based on the given criteria. (Children showing drug-induced facilitation of performance ≥ 25% (i.e. a 25% drop in error rate) compared with baseline or placebo were classified as favourable responders, whereas those whose performance did not improve to this extent were classified as non-responders)<br><br>Treatment compliance: Rapport 1987 and DuPaul 1993 (in Rapport 1987): Both used and unused envelopes were returned to the Rhode Island Construction Leadership Council (CLC) on a weekly basis to assess medication compliance. DuPaul 1993 and Denney 1999 (in Rapport 1987): Medication was properly administered nearly 100% of the time, with "make-up" observation days scheduled after rare occasions when compliance was not obtained |
| Outcomes | **ADHD symptoms**<br><br>1. Abbreviated Conners' Teacher Rating Scale: once each week (1.5 to 2 hours after morning medication)<br><br>**Non-serious adverse events**<br><br>1. Data from the Subjective Treatment Emergent Symptom Scale (no data reported on this scale. Additional data cannot be obtained from study authors)<br>2. Kelly 1988 (in Rapport 1987) measured heart rate. Each child's resting heart rate (average beats per minute) was measured for 5-minute periods at 3 intervals (immediately before oral ingestion of methylphenidate or placebo (IV), 120 minutes post ingestion and 180 minutes post ingestion). Each of these measurements was taken at the same relative time of day (between 2:00 PM and 6:00 PM) and on the same day of each week throughout the 6-week course of the study |

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| **Notes** | Sample calculation: no<br><br>Ethics approval: not stated. From Kelly 1988 in Rapport 1987: believe the study was approved by the Institutional Review Board IRB at the University of Rhode Island (the site of the study), but Dr. Rapport could confirm this (Ramstad 2013c [pers comm])<br><br>**Key conclusions of study authors**<br><br>1. Group results showed significant medication effects on classroom percentage of on-task behaviour, academic efficiency, teacher ratings of attention and continuous performance task omission errors<br>2. Results indicate that higher dosages are linearly related to increasing levels of rate, and that these effects are dependent upon both the initial heart rate value and the time course of medication<br>3. Methylphenidate had a significant effect on classroom measures of attention and academic efficiency, which were similar to those of normal control children. Still 25% of the sample failed to show normalised levels of classroom performance<br>4. Results of the present investigation show that methylphenidate effects were generally rate-dependent in the classical fashion (i.e. negative linear relationship between control response rate and output ratio) for responding that was controlled by schedules, which engendered both low and high response rates<br><br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; excluded methylphenidate non-responders<br><br>Any withdrawals due to adverse events: not stated<br><br>Email correspondence with study author: We contacted Dr. Rapport by email (Ramstad 2013c [pers comm]). He has stated that he does not have any supplementary data except those provided in these articles. We also contacted Dr. DuPaul (Ramstad 2013b [pers comm]) |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Rapport 1987: All children received each of the 5 methylphenidate doses in a randomly assigned counterbalanced sequence |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Unclear risk | All methylphenidate and placebo doses were packaged in coloured gelatin capsules by the clinic's pharmacist. Capsules were sealed in individual daily-dated envelopes. All teachers were blinded as to time of administration and specific dose |
| Blinding of outcome assessment (detection bias) | Unclear risk | No information |
| Incomplete outcome data (attrition bias) | High risk | Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): yes (4 participants) |
| Selective reporting (reporting bias) | Unclear risk | No information |
| Vested interest bias | Unclear risk | Study was not supported by any funding, either external or internal. This project was supported in part by a Biomedical Research Support Grant (no. S07 RR05712), which was awarded to the first study author by the Biomedical Research Support Grant Program, Division of Research Resources, National Institutes of Health<br><br>Conflicts of interest: no information |

*Rapport 2008*

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| **Methods** | Double-blind, placebo-controlled, 5-week, cross-over trial with 2 interventions<br>1. Methylphenidate (5 mg, 10 mg, 15 mg and 20 mg)<br>2. Placebo<br>Phases: baseline (1 week) and 5 cross-over phases (1 week placebo and 1 week methylphenidate each) |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 65. Participants were randomly assigned to 1 (of not stated) possible drug condition order<br>Number of participants followed up: 65 (58 boys, 7 girls)<br>Number of withdrawals: none<br>Diagnosis of ADHD: DSM-IV (all were of the combined subtype)<br>Age: mean 8.56 years (SD 1.25; range 6 to 11)<br>IQ: mean 102.8 (SD 10.0; range not stated)<br>Methylphenidate naive: Eight had experienced brief trials of stimulant therapy within the previous 4 years. None were prescribed psychostimulants immediately before the start of the current study<br>Ethnicity: Caucasian (100%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: low to middle<br>**Inclusion criteria**<br>1. ADHD diagnosis confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia<br>2. Problems in ≥ 50% of the situations on the Barkley Home Situations Questionnaire<br>3. Maternal rating ≥ 2 SD above the mean on the Werry-Weiss-Peters Activity Scale<br>4. Teacher rating on the ADD/H Comprehensive Teacher Rating Scale ≥ 2 SD above the mean<br>**Exclusion criteria**<br>1. Conduct disorder; gross neurological, sensory or motor impairment |
| **Interventions** | Participants were randomly assigned to different possible drug condition orders of immediate-release methylphenidate (5 mg/d, 10 mg/d, 15 mg/d, 20 mg/d) and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: once daily, in the morning<br>Duration of each medication condition: 1 week<br>Washout before study initiation: None were prescribed psychostimulants immediately before the start of the current study<br>Medication-free period between interventions: 1 day<br>Titration period: none<br>Treatment compliance: "nearly 100%; envelopes were returned on a weekly basis" |
| **Outcomes** | **Non-serious adverse events**<br>1. Subject's Treatment Emergent Symptoms Scale of National Institute of Mental Health (NIMH) (adjusted to children for the children): rated weekly by observer interviewing parent and child |

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| Notes | Sample calculation: not stated<br>Ethics approval: yes<br>**Comments from study authors**<br>1. Increased frequency and/or severity of emergent symptoms reported by or observed in children receiving psychostimulant therapy are probable to the extent that dosing regimens differ from the parameters reported herein, particularly for symptoms highly specific to methylphenidate, that is, children receiving multiple doses per day, single doses exceeding 20 mg, different methylphenidate formulations and methylphenidate over a longer duration of time are likely to experience greater frequency and/or severity of emergent symptoms<br>2. Immediate-release methylphenidate formulary is currently used less frequently than that of newer formulations, and the generalisability of present findings to long-duration, sustained-release and other variants is unknown<br>**Key conclusion of study authors**<br>1. Collectively, our findings point to a clear need to develop psychometrically sound treatment-emergent symptom rating scales for the purposes of monitoring physical and behavioural complaints of children treated with psychostimulants<br>**Comment from review authors**<br>1. Study authors used a design with a once-daily, immediate-release preparation of methylphenidate. This seems to be exceptional compared with other studies<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: no<br>Email correspondence with study authors: April 2014. Obtained supplemental information regarding data |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | By email: We used a computer-generated random assignment (without replacement) procedure with an additional stipulation that a nearly equal number of children had to be assigned to each of the possible drug condition orders. Children were entered onto the list as they entered the study and followed that particular order (of which coders, parents, teachers and evaluators were unaware throughout the study) ( Magnusson 2014b [pers comm] ) |
| Allocation concealment (selection bias) | Low risk | Same as above |
| Blinding of participants and personnel (performance bias) | Low risk | Methylphenidate and placebo dosages were packaged in coloured gelatin capsules by the clinic's pharmacist to avoid detection of dose and taste |
| Blinding of outcome assessment (detection bias) | Low risk | Rater was blinded |
| Incomplete outcome data (attrition bias) | Low risk | Information received by email: no drop-outs (Magnusson 2014b [pers comm])<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Low risk | All outcomes are reported |
| Vested interest bias | Low risk | None<br>Conflicts of interest: no financial, corporate or commercial relationships to disclose |

### *Riggs 2011*

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| **Methods** | Sixteen-week, randomised, 11-centre, parallel-group trial with 2 arms<br>1. OROS methylphenidate<br>2. Placebo<br>Participants in both medication groups received manual-standardised, individual cognitive-behavioural therapy through motivational enhancement approaches throughout the 16-week medication trial |
| **Participants** | Number of participants screened: 1334<br>Number of participants included: 303 (239 boys, 64 girls)<br>Number of participants randomly assigned: methylphenidate 151, placebo 152<br>Number of participants followed up in each arm: methylphenidate 151, placebo 152<br>Number of withdrawals in each arm: methylphenidate 33, placebo 43<br>Diagnosis of ADHD: DSM-IV (combined (68.6%), hyperactive-impulsive (2.6%), inattentive (28.1%))<br>Age: mean 16.5 years (SD 1.3; range 13 to 18)<br>IQ: All participants were cognitively normal<br>Methylphenidate naive: not stated<br>Ethnicity: Hispanic (15.2%)<br>Race: Caucasian (61.7%), African American (23.2%), Asian (1.3%), Native American/Alaskan (1.0%), other (12.7%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: major depressive disorder (12.5%), conduct disorder (32.3%), non-nicotine substance use disorder (100%) |

Comedication: drug/alcohol use

Sociodemographics: not stated

**Differences between groups**

1. No statistically significant differences in baseline demographics were noted between the 2 groups

**Inclusion criteria**

1. Meets DSM-IV diagnostic criteria for ADHD
2. Meets DSM-IV diagnostic criteria for ≥ 1 non-nicotine substance use disorder
3. DSM-IV ADHD Symptom Checklist score ≥ 22 derived from the adolescent-completed checklist

**Exclusion criteria**

1. Serious medical illness or cardiac illness
2. History of tic disorder*
3. Pregnant or breastfeeding
4. Meets DSM-IV criteria for current or lifetime psychotic disorder
5. Meets DSM-IV criteria for current or lifetime bipolar disorder
6. Requires/or prescribed other concurrent psychotropic medication
7. Taking any medications that may produce interactions with OROS methylphenidate

Opiate dependence

1. Methamphetamine abuse, dependence or past month use
2. Suicidal risk
3. Enrolled in an in-patient, residential, day treatment or out-patient substance abuse programme within 28 days before signing consent
4. Participation in other substance or mental health treatment

**Exploratory analyses of treatment response (ADHD-RS)**

1. ADHD subtypes
   a. Defined according to DSM-IV criteria (i.e. inattentive subtype with ≥ 6 inattentive symptoms and not ≥ 6 hyperactive-impulsive symptoms)
      i. Number of participants excluded: 13 because they did not meet criteria for a subtype, 14 because they did not meet criteria for hyperactive-impulsive subtype
      ii. Number of participants included: inattentive subtype 103, combined subtype 173. Subtypes did not differ with regard to age or ethnicity but did differ with regard to sex, comorbid conduct disorder, inattentive and hyperactive-impulsive symptoms and dependence diagnoses
   b. More strictly defined subtypes (i.e. strict inattentive subtype with ≥ 6 inattentive symptoms and ≤ 3 hyperactive-impulsive symptoms; strict combined type with ≥ 6 inattentive symptoms and ≥ 8 hyperactive-impulsive symptoms)
      i. Number of participants included: inattentive subtype 52, combined subtype 97
2. Major depressive disorder comorbidity
   a. 38 participants with major depressive disorder, 265 without major depressive disorder
   b. Number of participants randomly assigned
      i. Methylphenidate: 19 with major depressive disorder, 133 without major depressive disorder
      ii. Placebo: 19 with major depressive disorder, 132 without major depressive disorder
   c. No significant differences between groups were noted with regard to ADHD symptom severity, comorbid conduct disorder or substance abuse or dependence diagnoses. Differences between groups were noted with regard to age, sex, court mandate to substance treatment and days of past-month non-nicotine substance use
3. Comorbid conduct disorder
   a. 299 participants included in this analysis. Four were excluded because they did not have a non-tobacco substance use disorder or did not meet inclusion criteria for ADHD
   b. Number of participants randomly assigned: methylphenidate 48 with conduct disorder, placebo 49 with conduct disorder

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| Interventions | Participants were randomly assigned to OROS methylphenidate or placebo<br>Mean methylphenidate dosage at the end of treatment: 68 mg<br>Administration schedule: single dose in the morning<br>Duration of intervention: 16 weeks<br>Titration period: 2 weeks post randomisation<br>Treatment compliance: 79% (pill counts), 82.3% (self reports) |
| Outcomes | **ADHD symptoms**<br>1. ADHD Rating Scale, clinician-administered, adolescent informant: rated at baseline and weekly for 16 weeks<br>2. ADHD Rating Scale, clinician-administered, parent informant: rated at weeks 8 and 16<br>**Serious adverse events**<br>1. Systematically assessed by medical clinicians during weekly visits<br>**Non-serious adverse events**<br>1. Systematically assessed by medical clinicians during weekly visits<br>2. Laboratory assessments ascertained at baseline and at 16 weeks included liver function testing, complete blood count with differential and urinalysis<br>3. Massachusetts General Hospital Abuse and Diversion Questionnaire, self administered and completed monthly<br>4. Massachusetts General Hospital Liking Scale completed at study weeks 4, 8, 12 and 16. Relevant subscales: feeling high, feeling depressed, craving medication, craving substances |

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| Notes | Sample calculation: yes; sample size of 300 participants was calculated for ADHD Rating Scale<br><br>Ethics approval: yes; Institutional Review Boards approved the protocol before participant enrolment<br><br>**Comments from study authors**<br><br>1. One participant did not meet diagnostic criteria for ADHD, and 1 did not have a score ≥ 22 on the ADHD Rating Scale, but both were included in analyses<br>2. Two participants did not meet diagnostic criteria for a non-tobacco substance use disorder but were included in analyses<br>3. Results of this study add to the growing suspicion that CBT (for SUD) may contribute to ADHD treatment response and warrants further investigation<br>4. Limitations: This study was not powered to address safety, and no current consensus exists regarding the most valid outcome measures for ADHD in adolescents with or without substance use disorder<br><br>**Key conclusions of study authors**<br><br>1. OROS methylphenidate did not show greater efficacy than placebo for ADHD or greater reduction in substance use among adolescents concurrently receiving individual cognitive-behavioural therapy for co-occurring substance use disorders<br>2. OROS methylphenidate was relatively well tolerated and was associated with modestly greater clinical improvement on some secondary ADHD and substance outcome measures<br>3. With good monitoring, and in the context of substance abuse treatment, OROS methylphenidate can be used safely in adolescents with a substance use disorder despite non-abstinence<br>4. Higher baseline use of alcohol and cannabis was associated with increased risk of experiencing a treatment-related adverse event with OROS methylphenidate, but baseline use did not increase the risk of serious adverse events or of any particular category of adverse events<br>5. For adolescent misuse/diversion of OROS methylphenidate, results suggest that OROS methylphenidate was not misused/diverted to a greater extent than placebo and was not impacted by baseline substance use severity<br>6. Despite baseline differences, both inattentive and combined subtypes responded equally to treatment, suggesting limited relevance for subtype designation in treatment planning<br>7. ADHD symptom severity (based on DSM-IV ADHD Rating Scale) followed a slightly different course of improvement, although with no differences between the group with comorbid major depressive disorder and the group without major depressive disorder in baseline or 16-week symptom severity, or in 16-week reduction: Presence of major depressive disorder was not associated with ADHD treatment response in this sample<br>8. Interaction effects showed that OROS methylphenidate improved substance use disorder outcomes among adolescents with comorbid conduct disorder compared with placebo<br>9. Although severe substance use disorder may require more intensive psychosocial treatment, OROS methylphenidate may improve substance treatment outcomes among adolescents with comorbid attention and conduct problems<br><br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br><br>**Comment from review authors**<br><br>1. Data are influenced by drug abuse, especially data on adverse events, but no statistically significant differences between OROS methylphenidate and placebo in self reported medication abuse were noted<br><br>Email correspondence with study authors: December 2013. We obtained supplemental information (IQ, allocation concealment and detailed description of 1 of the serious adverse events) |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomly assigned to OROS methylphenidate or matching placebo in a 1:1 ratio, stratified by site and completed by computer at a centralised location |
| Allocation concealment (selection bias) | Low risk | Product was supplied in pre-randomly assigned kits containing individual bottles. Kits and bottles were labelled with the protocol number and treatment/randomisation number. Labeling protected the study, ensuring that it remained blinded, and indicated that the medication was investigational |
| Blinding of participants and personnel (performance bias) | Low risk | Sites were provided blinded medication bottles for each randomly assigned participant<br>Masking: double-blinded (participant, caregiver, investigator, outcomes assessor) |
| Blinding of outcome assessment (detection bias) | Low risk | Masking: double-blinded (participant, caregiver, investigator, outcomes assessor) |
| Incomplete outcome data (attrition bias) | Low risk | Primary analyses were ITT, including all randomly assigned study participants<br>Completers (N = 227) were not different from non-completers (N = 76) in baseline demographic or clinical characteristics, and the proportion of completers did not differ by treatment assignment |
| Selective reporting (reporting bias) | Low risk | No major violation compared with CT.gov<br>All pre-specified outcomes of interest have been reported |
| Vested interest bias | Unclear risk | OROS methylphenidate and matching placebo were supplied to the Clinical Trials Network contract pharmacy (EMINENT Services Corporation) by McNeil Consumer and Specialty Pharmaceuticals (distributor for Concerta), at no cost<br>Principal investigators are NOT employed by the organisation sponsoring the study. NO agreement between principal investigators and study sponsor (or its agents) restricts the principal investigator's rights to discuss or publish trial results after the trial is complete<br>Conflicts of interest: Some study authors have received research support from, served on Speakers' Bureaus of or acted as consultants for pharmaceutical companies |

*Rubinsten 2008*

| Methods | Five-day, randomised, double-blind, placebo-controlled, cross-over trial with 4 interventions and 11 possible orders<br>1. Methylphenidate, in 3 different dosages<br>2. Placebo |
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| Participants | Number of participants screened: 170<br>Number of participants included: 18. Participants were randomly assigned to 1 of 11 possible drug condition orders<br>Number of participants followed up: 18 (15 boys, 3 girls)<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-IV (combined (28%), hyperactive-impulsive (0%), inattentive (72%))<br>Age: mean 9.73 years (range not reported)<br>IQ: mean 104.44<br>Methylphenidate naive: 0%<br>Ethnicity: not stated<br>Country: Canada<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: no<br>Sociodemographics: no information<br>**Inclusion criteria**<br>1. Completed the same research protocol in an acute, randomised placebo-controlled, cross-over trial<br>2. IQ ≥ 82<br>3. No current evidence on or history of neurological dysfunction, poor physical health, uncorrected sensory impairments or history of psychosis<br>4. At least average reading scores<br>5. ADHD according to DSM-IV<br>6. One group of patients needed to have a score < 79 (n = 6)<br>a. One group had a score between 80 and 89 on the Wide Range Achievement Test (n = 6 of 9 meeting criterion)<br>b. One group had a score ≥ 90 on the Wide Range Achievement Test (n = 6 of 83 meeting criterion)<br>7. Free of medication for minimum of 24 hours before diagnostic assessment and participation in the medical trial<br>**Exclusion criteria**<br>1. Not stated |
| Interventions | Participants were randomly assigned to 1 of 11 possible drug condition orders of methylphenidate (10 mg, 15 mg and 20 mg) and placebo<br>Mean methylphenidate dosage: 0.27 mg/kg, 0.42 mg/kg and 0.58 mg/kg, respectively<br>Administration schedule: not stated<br>Duration of each medication condition: 1 day<br>Washout before study initiation: 24 hours<br>Medication-free period between interventions: not stated<br>Titration period: none<br>Treatment compliance: not stated |
| Outcomes | **Non-serious adverse events**<br>1. Examiner observed the child for possible side effects of medication |

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| **Notes** | Sample calculation: no<br>Ethics approval: not stated<br>**Comment from study authors**<br>1. This was a sample of small children, so we do not know whether the same results would hold for adolescents or adults<br>**Key conclusion of study authors**<br>1. We found clear dissociation of methylphenidate functions: Methylphenidate improved working memory functions but did not improve specific cognitive functions such as quantity manipulation. Moreover, methylphenidate showed decreased efficacy for arithmetic performance in ADHD + developmental dyscalculia, highlighting the need for additional intervention in this subgroup<br>**Comment from review authors**<br>1. Study authors selected 12 patients from a larger population but did not describe how this was done<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Master randomisation tables were prepared by the research support pharmacist at the hospital using simple randomisation with restrictions. A balanced block 22 design was used |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | Examiner, psychiatrist, child and child's family were not informed about the child's randomisation order or daily medication status until trial completion. Placebo and active medication were prepared by the hospital pharmacist as powdered and packaged in an opaque gelatin capsule to prevent identification of content by colour, taste or volume. Each child's medication was placed in an individually named and dated envelope to ensure accurate administration |
| Blinding of outcome assessment (detection bias) | Low risk | Examiner, psychiatrist, child and child's family were not informed about the child's randomisation order or daily medication status until trial completion. |
| Incomplete outcome data (attrition bias) | Low risk | No drop-outs |
| Selective reporting (reporting bias) | Unclear risk | No information |
| Vested interest bias | Low risk | Research was completed while Dr. Rubinsten was a post-doctoral fellow at the Hospital for Sick Children (HSC), in Toronto, Canada, and was supported by the Rothschild Fellowship from Israel. It was undertaken, in part, through funding received from the Canadian Institutes of Health (CIHR: Grant #MOP 64312), a CIHR post-doctoral fellowship (A-CB), and the Canada Research Chairs Program (RT) |

*Samuels 2006*

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| **Methods** | Double-blind, randomised, cross-over trial with 2 interventions<br>1. Methylphenidate<br>2. Placebo<br>Phases: 2 |

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| Participants | Number of participants screened: not stated<br>Number of participants included: 6. Participants were randomly assigned to 1 (not stated) possible drug condition order<br>Number of participants followed up: not stated<br>Number of withdrawals: not stated<br>Diagnosis of ADHD: DSM-IV (subtype not stated)<br>Age: mean (not stated)<br>IQ: mean (not stated)<br>Sex: not stated<br>Methylphenidate naive: not stated<br>Ethnicity: Caucasian (100%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Children 5 to 15 years of age<br>2. Long-term stable dose of stimulant medicine for treatment of ADHD<br>3. Recruited from local private paediatrician and psychiatric offices<br>**Exclusion criteria**<br>1. Receiving concomitant medication that might increase blood pressure<br>2. Documented hypertension requiring antihypertensive therapy |
| Interventions | Participants were randomly assigned to 1 (not stated) possible drug condition order of (not stated) methylphenidate and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: Each child was kept on his or her previous regimen of treatment and a corresponding placebo<br>Duration of each medication condition: 24 hours<br>Washout before study initiation: 3-day run-in<br>Titration period: Children were kept on stable medication doses and schedules<br>Treatment compliance: not stated |
| Outcomes | **Non-serious adverse events**<br>1. 24-hour ambulatory blood pressure monitoring (ABPM) was performed on and off medication<br>No separate data were available for methylphenidate |
| Notes | Sample calculation: no<br>Ethics approval: not stated<br>**Key conclusion of study authors**<br>1. This study provides evidence of a possible negative cardiovascular effect of stimulant medications in children with ADHD. This potential cardiovascular risk should be balanced against the beneficial behavioural effects of this class of medication<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: July 2014. Emailed study authors to ask for additional information but have not received a reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not described; "randomized in double-blind fashion" |
| Allocation concealment (selection bias) | Unclear risk | "Randomized in double-blind fashion" |
| Blinding of participants and personnel (performance bias) | Low risk | Described as "double-blind". All medications and placebo were identically packaged by the research pharmacy |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not stated |
| Incomplete outcome data (attrition bias) | High risk | Only participants who successfully underwent an ambulatory blood pressure monitoring study at the end of each phase were included in the primary analyses |
| Selective reporting (reporting bias) | Unclear risk | Protocol not found |
| Vested interest bias | Unclear risk | Not stated<br>Conflicts of interest: not declared |

*Schachar 1997a*

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| **Methods** | Twelve-month, parallel RCT with 4 arms<br>1. Methylphenidate + parent training<br>2. Methylphenidate + parent support<br>3. Placebo + parent training<br>4. Placebo + parent support<br>Follow-up at baseline (before treatment), at end of titration (3 to 4 weeks) and after 4, 8 and 12 months of treatment<br>Follow-up study of cohort completing the 12-month RCT: Participants were evaluated annually for 5 years |

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| Participants | Number of participants screened: 302<br>Number of participants included: 91 included in the RCT (methylphenidate: 37 boys, 9 girls; placebo: 37 boys, 8 girls)<br>Number of participants randomly assigned: methylphenidate 46, placebo 45<br>Number of participants followed up: methylphenidate 45, placebo 18<br>Number of withdrawals: methylphenidate 1, placebo 27<br>Diagnosis of ADHD: DSM-III-R diagnosis of ADHD (subtype not stated)<br>Mean age: methylphenidate 8.4 years, placebo 8.3 years (range 6 to 12)<br>IQ: mean (methylphenidate 110.3; placebo 107.6)<br>Methylphenidate naive: 100%<br>Ethnicity: not stated<br>Country: Canada<br>Setting: research unit at hospital.<br>Comorbidity: oppositional defiant disorder (methylphenidate 56.5%, placebo 44.4%), conduct disorder (methylphenidate 6.5%, placebo 20.0%), anxiety (methylphenidate 21.7%, placebo 24.4%)<br>Comedication: no<br>Sociodemographics: Placebo group had a higher score at baseline for psychosocial adversity than those assigned to the methylphenidate group<br>Psychosocial risk index: methylphenidate 1.5%, placebo 2.7%<br>**Inclusion criteria**<br>Screening<br>1. Age between 6 and 12 years<br>2. ≥ 6 of 14 ADHD symptoms on the ADHD Rating Scale (DuPaul 1991a)<br>3. Parental report of some ADHD symptoms at school<br>4. No previous treatment with methylphenidate<br>5. Willingness to participate in a study that involved random assignment to treatments for ADHD (both pharmacological and non-pharmacological)<br>6. ≥ 1 parent able to communicate in English.<br>Diagnostic evaluation<br>1. Exhibit pervasive ADHD, defined as ≥ 8 of the 14 DSM-III-R criteria for ADHD, in 1 setting (at home on the PICS, or at school on the Teacher Telephone Interview (prepared by study authors)) and ≥ 5 ADHD criteria in the other setting<br>2. History of ADHD symptoms of ≥ 6 months' duration before the age of 7 years<br>Final inclusion criteria<br>1. Exhibit pervasive ADHD, defined as ≥ 8 of the 14 DSM-III-R criteria for ADHD in 1 setting and ≥ 5 ADHD criteria in the other setting<br>2. History of ADHD symptoms of ≥ 6 months' duration before the age of 7 years<br>3. Estimated full-scale IQ > 80<br>4. No primary anxiety or affective disorder<br>**Exclusion criteria**<br>1. Attending a full-time residential or day treatment programme<br>2. Has received regular medication for a medical problem<br>3. Chronic medical condition including a severe motor or vocal tic disorder and Tourette's syndrome<br>4. Prior treatment for tics |

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| Interventions | Randomly assigned to 1 of the 4 treatment groups after stratification based on comorbid, conduct or oppositional disorder: methylphenidate + parent training/parent support, placebo + parent training/parent support<br>Titration period: 3 to 4 weeks (depending on child's weight) after randomisation<br>Mean methylphenidate dosage: target dose 0.7 mg/kg body weight, twice daily<br>Administration schedule: breakfast and lunch<br>Duration of intervention: 12 months<br>Treatment compliance: methylphenidate 80%, placebo 64% |
| Outcomes | **ADHD symptoms**<br>1. Parent- and teacher-rated IOWA Conners' Rating Scale at baseline, at end of titration and at 4 months<br>**General behaviour**<br>1. Parent- and teacher-rated telephone interview probe (TIP) (Corkum, personal communication, 1992) questionnaire at baseline and at 4 months. Grouped into 4 factors: inattention, hyperactivity-impulsivity, oppositional behaviour, difficulty experienced by rater in dealing with typical daily problem situations<br>**Non-serious adverse effects**<br>1. Parent- and teacher-rated questionnaire with 14 common side effects (modified from Barkley 1990) administered by telephone at baseline, at end of titration and at 4 months. Grouped into 4 factors: affective, overfocusing, physiological and tics. Parent-rated questionnaire with 16 possible adverse effects (also modified from Barkley 1990) at annual evaluations (telephone interviews)<br>2. Height and weight were measured at baseline, at week 3 to 4 and at 4 months in the RCT, and annually in the follow-up study. Standing height was measured in centimeters without shoes from floor to vertex of head. Weight in indoor clothing, without shoes, was measured in kilograms. Baseline and annual measures of height and weight were ascertained with the same stadiometer<br>3. Presence and severity of tics were rated at baseline, end of titration, 4 months, 8 months and 12 months by research assistants interviewing parents and teachers. Moderate and severe Tourette's-like symptoms were assessed and diagnosed by the supervising psychiatrist |

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| Notes | Sample calculation: yes<br><br>Ethics approval: yes<br><br>**Comments from study authors**<br><br>1. Current RCT is limited by sample size and by medium statistical power<br>2. This cannot be generalised to situations in which higher doses of methylphenidate may be used, or to children with more than moderate tics<br>3. Instrument used to measure adverse effects was originally designed for short-term pharmacological studies and could fail to identify potentially long-term health concerns in the follow-up study<br>4. Sample in the follow-up study of previous participants in an RCT would be biased in favour of adherence relative to a cohort chosen and followed from the time of identification<br>5. Infrequent contact with participants and lack of an untreated control group are additional limitations of the follow-up study<br>6. Study did not include pubertal staging<br><br>**Key conclusions of study authors**<br><br>RCT<br><br>1. Positive effects of methylphenidate on behaviour are evident in the classroom, but with methylphenidate given twice daily, parents did not report that methylphenidate improved behaviour at home<br>2. Comorbid anxiety did not appear to influence development of side effects or behavioural response to methylphenidate when dose was titrated as in standard clinical practice<br>3. Doses of methylphenidate based on the typical clinical titration procedure did not produce significantly more tics than placebo in children with or without pre-existing (mild to moderate) tics<br><br>Follow-up study<br><br>1. Psychostimulants improve ADHD symptoms for up to 5 years, but adverse effects persist<br>2. Long-term use of high doses of stimulants during a period of 1 to 5 years is likely to have measurable effects on rate of growth in school-aged children with attention deficit hyperactivity disorder<br><br>**Comments from review authors**<br><br>1. Thiruchelvam 2001 reported no relevant outcome measures for our review; the article was therefore excluded during the full-text reading process<br>2. Corkum 1999 was excluded during the abstract reading process<br>3. Data in both Schachar 1997 and Diamond 1999 are preliminary (interim results of first 4 months of treatment). Data from the 2 placebo groups (cointervention: parent training and parent support) and the 2 methylphenidate groups (same 2 cointerventions) are combined (placebo vs methylphenidate). No final report focuses on ADHD symptoms<br>4. As participants are allowed to switch from the allocated intervention group during the study, we can use only data regarding adverse effects<br><br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br><br>Email correspondence with study authors: September to October 2013. Unfortunately, they were not able to provide supplemental data |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomly assigned after stratification based on the presence of comorbid conduct or oppositional disorder and assigned to 1 of the 4 treatment groups. Randomly assigned based on a random number table |
| Allocation concealment (selection bias) | Low risk | Concealed from the physician and participants before randomisation and maintained throughout the study |
| Blinding of participants and personnel (performance bias) | Low risk | All participants (child, research staff, parents and teachers) were blinded to the medication assignment |
| Blinding of outcome assessment (detection bias) | Low risk | All participants (child, research staff, parents and teachers) were blinded to the medication assignment |
| Incomplete outcome data (attrition bias) | High risk | No imputation method: The effect of treatment was analysed among participants who adhered to their original medication assignment. At the 4-month point, children not taking any medication were grouped with those taking placebo. When a participant switched from placebo to methylphenidate treatment, they were counted within the methylphenidate group<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | Not possible to find protocol |
| Vested interest bias | Unclear risk | Medical Research Council of Canada, National Health Research Development Program of Canada and the Department of Psychiatry, The Hospital for Sick Children, Toronto. Placebo pills were provided by Ciba Geigy, Canada, Ltd<br>Conflicts of interest: Two study authors have reported working as consultants for pharmaceutical companies, and 1 has furthermore received industry-sponsored research grants |

*Schachar 2008*

| Methods | Single-centre, randomised, double-blind, 3-way cross-over trial with 2 interventions<br>1. Methylphenidate (immediate-release or extended-release)<br>2. Placebo<br>Phases: immediate-release and multi-layer-release |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 18<br>Number of participants followed up: 17 (15 boys, 2 girls)<br>Number of withdrawals: 1<br>Diagnosis of ADHD: DSM-IV diagnosis of ADHD (combined (100%))<br>Age: mean 11.3 years (range 6.8 to 15.3)<br>IQ: ≥ 85<br>Methylphenidate naive: 5 (29.4)<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: no<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. 6 to 15 years of age<br>2. IQ ≥ 85 within previous 12 months<br>3. Mentally and physically competent to provide written informed consent<br>4. Ability to read, speak and understand English<br>5. Otherwise able to comply with study protocol<br>**Exclusion criteria**<br>1. Allergic to methylphenidate or amphetamines, or had a history of serious adverse reactions to methylphenidate or lack of response to methylphenidate<br>2. Serious or unstable medical illness, comorbid psychiatric illness of sufficient severity to require treatment or currently receiving psychotropic medications or herbal treatments<br>3. Disorders of the sensory organs (particularly deafness), autism, psychosis or any unstable psychiatric conditions |
| Interventions | Participants were randomly assigned to 1 of 2 possible drug condition orders of immediate-release and extended-release methylphenidate and placebo<br>Mean methylphenidate dosage: 31.2 mg/d (SD 11.7 mg/d; range 20 to 60 mg/d), 1.2 mg/kg<br>Administration schedule: twice daily, in the morning and at noon (4 hours apart)<br>Duration of each medication condition: 6 days<br>Washout before study initiation: 1 day<br>Titration period: none. Participants who were receiving methylphenidate at the time of study entry received the dose of methylphenidate that they were taking before entry into the study/duration initiated before/after randomisation<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. IOWA: parent-rated weekly (8 times in 1 day)<br>2. Conners' Continous Performance Task: rated weekly (8 times in 1 day)<br>**Non-serious adverse events**<br>1. Clinical Assessment of Side Effects Scale: parents and teachers separately, rated weekly 1 day before other assessments<br>2. Spontaneously reported adverse events: investigator, collected weekly |

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| **Notes** | Sample calculation: no<br>Ethics approval: yes<br>**Key conclusion of study authors**<br>1. Both MLR methylphenidate and immediate-release methylphenidate compared with placebo demonstrated significant improvement on IOWA-C average total score, with onset of action observable by 1 hour<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes<br>Email correspondence with study authors: May 2014. Emailed study authors to ask for supplementary information but have not received a reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomly assigned to a treatment sequence according to a Latin square |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Unclear risk | Double-blind; not further described |
| Blinding of outcome assessment (detection bias) | Unclear risk | Double-blind; not further described |
| Incomplete outcome data (attrition bias) | High risk | All enrolled participants with data from all 3 treatment phases who did not have major protocol violations were considered evaluable for efficacy; all participants were evaluated for safety |
| Selective reporting (reporting bias) | Low risk | No protocol was published. All pre-specified outcomes of interest have been reported |
| Vested interest bias | High risk | Study was funded by Purdue Pharma (Canada)<br>Conflicts of interest: Some study authors are working for Purdue Pharma |

*Schulz 2010*

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| **Methods** | Double-blind, randomised, multi-centre, triple cross-over design with 3 interventions<br>1. Methylphenidate - Ritalin LA 20 mg once daily<br>2. Methylphenidate - Medikinet Retard 20 mg once daily<br>3. Placebo |

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| Participants | Number of patients screened: 147<br>Number of participants included: 147<br>Number of participants randomly assigned: not stated<br>Number of participants followed up: 139<br>Number of withdrawals: 1<br>Diagnosis of ADHD: DSM-IV diagnosis (combined (55%), hyperactive-impulsive (8%), inattentive (37%))<br>Age: mean 10.2 years (range 6 to 14)<br>IQ: not stated<br>Sex: 119 boys, 28 girls<br>Methylphenidate naive: 0%<br>Ethnicity: not stated<br>Country: Germany<br>Setting: out-patient clinic<br>Comorbidity: 6.8% (disturbance in social behaviour (2.7%), initial insomnia (0.7%), oppositional defiant disorder (1.36%), dysphemia (0.68%), encopresis (0.68%))<br>Comedication: no<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. DSM-IV diagnosis of ADHD confirmed by Kiddie Schedule for Affective Disorders and Schizophrenia in the German Version (Delmo et al. 2000)<br>2. All children had to be on a stable and well-tolerated dose of 20 mg-equivalent methylphenidate for ≥ 1 month before screening<br>**Exclusion criteria**<br>1. Patients with known previous non-response to methylphenidate<br>2. Children with relevant somatic or psychiatric comorbidity requiring pharmacological treatment (e.g. psychosis, major depression)<br>3. Patients with warnings as described in the prescribing information for Ritalin LA, including tic disorders |
| Interventions | Pre-randomisation phase and 3 treatment periods of 7 days each. Participants were randomly assigned to 1 of 6 possible drug condition orders of 20 mg Ritalin LA methylphenidate, 20 mg Medikinet Retard methylphenidate and placebo<br>Mean methylphenidate dosage: 20 mg daily<br>Administration schedule: once daily, morning<br>Time points: 9:00 AM<br>Duration of each medication condition: 7 days<br>Washout before study initiation: none<br>Medication-free period between interventions: none<br>Titration period: none<br>Treatment compliance: not stated |

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| Outcomes | **ADHD symptoms**<br>1. Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP) Scale (Wigal 1998) by 3 treatment-blinded observers: rated at 1.5, 3.0, 4.5, 6.0 and 7.5 hours after drug intake at the end of each treatment week<br>**General behaviour**<br>1. Nisonger Child Behavior Rating Form (NCBRF-TIQ) to assess behaviour in children (Aman 2002): applied once at the end of each treatment period<br>**Serious adverse events**<br>1. One serious adverse event was reported: a case of acute appendicitis during treatment with Ritalin LA. This was judged to be not treatment related<br>2. Four events were reported as "severe" and drug-related: placebo: 2× aggressive behaviour; placebo: 1× lack of attention; Medikinet: 1× aggressive behaviour<br>**Non-serious adverse events**<br>1. Monitoring and recording of all adverse events (AEs) by<br>a. "Non-directive questioning" at every visit<br>b. "Regular monitoring of vital signs"<br>c. Participant were called by phone every midweek and were asked about adverse events<br>d. Clinical abnormality in blood pressure defined as increase or decrease ≥ 20 mmHg from age-dependent normal values (ages 6 to 9: systolic blood pressure (SBP) 90 mmHg, diastolic blood pressure (DBP) 60 mmHg; age > 10 years: SBP 110 mmHg, DBP 75 mmHg)<br>Clinically notable increased values for SBP were recorded under all 3 treatments: 15% on placebo, 17% on Ritalin LA and 18% on Medikinet. Abnormal increases in DBP were noted in 5% of patients taking placebo and Ritalin and in 3% of patients given Medikinet. Abnormal values in SBP among participants who had normal values at screening and at baseline were recorded in only 7 participants (3 given placebo, 3 taking Medikinet and 2 taking Ritalin LA - as reported in the article). Changes in vital signs were attributed to sympathomimetic effects of methylphenidate and were not considered clinically relevant |
| Notes | Sample calculation: yes<br>Ethics approval: yes<br>**Comments from study authors**<br>1. Another factor to be considered a limitation is that all participants were known methylphenidate responders. This decision was made to ensure that study objectives regarding efficacy were met. However, it might have led to overestimation of treatment effect and tolerability in the overall population, as no treatment-naive participants were included in this trial<br>2. Individual dose titration as a standard approach in everyday practice was not allowed during this trial; therefore treatment response might not have been optimal for all children<br>3. Inclusion of many other children, all with ADHD, as well as other experimental factors might have influenced the behaviour of the individual child<br>4. Encapsulation might have altered the pharmacokinetics of active substances<br>**Key conclusions of study authors**<br>1. Compared with placebo, both Ritalin LA and Medikinet Retard demonstrated robust treatment effects on core inattentive and hyperactive symptoms for up to 7.5 hours in children with ADHD in a laboratory classroom<br>2. Treatment with Ritalin LA and Medikinet Retard was generally well tolerated<br>3. No participant had to discontinue participation in the trial because of adverse events<br>4. Although almost every third participant was affected by ≥ 1 adverse event, almost all adverse events were of mild intensity<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; efficacy trial to prove non-inferiority of Ritalin LA vs Medikinet Retard. Highly restrictive inclusion criterion - responders only. Study authors acknowledge "it might overestimate the treatment effect and the tolerability in the overall population, as no treatment naive patients have been included in this trial" |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "Randomization was centrally generated with a validated system that automated the random assignment of treatment sequences to randomization numbers in a specified ratio" |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | "All treating physicians, other site staff, and patients, as well as data analysts and Novartis in-house personnel, remained blinded from the time of randomization until database lock. The raters also did not have access to information about adverse events to maintain the blind"; "To ensure blinding of the study, all capsules were overencapsulated in an identical optical design" |
| Blinding of outcome assessment (detection bias) | Low risk | "The scale was rated by three treatment-blinded observers in the classroom who were specifically trained on the SKAMP scale" |
| Incomplete outcome data (attrition bias) | Low risk | All randomly assigned participants were included in the intention-to-treat (ITT) population. Missing values for the primary endpoint were replaced by the worst value observed in another participant under the same treatment at the same assessment time. For non-inferiority comparisons, the per-protocol (PP) population consisting of participants without major protocol violations was considered primary<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Unclear risk | No information |
| Vested interest bias | High risk | Trial aimed at showing efficacy of Ritalin LA with purpose of obtaining marketing authorisation<br>Conflicts of interest: Almost all study authors have received grants, research support or other kinds of financial support from the medical industry |

*Schwartz 2004*

| Methods | Two-week, double-blind, placebo-controlled, cross-over, randomised clinical trial with 2 interventions<br>1. Methylphenidate<br>2. Placebo |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 44 (37 boys, 7 girls)<br>Number of participants followed up: 44<br>Number of withdrawals: none<br>Diagnosis of ADHD: DSM-IV (subtype not stated)<br>Age: mean 9.2 years (range 6 to 12)<br>IQ: > 70<br>Methylphenidate naive: 16<br>Ethnicity: not stated<br>Country: Canada<br>Setting: out-patient clinic<br>Comorbidity: conduct disorder (39%), oppositional defiant disorder (32%), separation anxiety disorder (16%), major depression (7%)<br>Comedication: no<br>Sociodemographics: income level category, mean 3.7<br>**Inclusion criteria**<br>1. ADHD diagnosis<br>**Exclusion criteria**<br>1. IQ < 70<br>2. Tourette's syndrome<br>3. Pervasive developmental disorder<br>4. Psychosis.<br>5. Taking any medication other than methylphenidate<br>6. Previous intolerance or allergic reaction to any psychostimulant |
| Interventions | Participants were randomly assigned to 1 of 2 possible drug condition orders of (0.5 mg/kg) methylphenidate and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: twice per day: morning/noon time points<br>Duration of each medication condition: 7 days<br>Washout before study initiation: yes (2 weeks)<br>Medication-free period between interventions: not stated<br>Titration period: none stated<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. Conners' Rating Scales - both teacher- and parent-rated<br>2. Restricted Academic Situation Scale<br>**Non-serious adverse events**<br>1. Actigraphic monitoring of sleep |

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| **Notes** | Sample calculation: post hoc power calculation<br>Ethics approval: yes<br>**Comment from study authors**<br>1. Good responder participants showed improvement in behaviour when taking methylphenidate but no difference in sleep-onset latency compared with those given placebo (average 49 minutes). However, this latency was rather long, and this was an open trial with no comparison group with poor or no response to methylphenidate<br>**Key conclusions of study authors**<br>1. Methylphenidate induces a 4% reduction in actigraph (slight but significant sleep disturbance)<br>2. Children who responded well to methylphenidate did not exhibit increased motor activity in sleep compared with those who did not respond or who responded poorly<br>3. Therapeutic efficiency does not come with more sleep side effects<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; exclusion of children with history of intolerance<br>Email correspondence with study authors: March to April 2014. We emailed study authors twice to ask for supplemental information regarding data on ADHD symptoms but have not received a reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
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| Random sequence generation (selection bias) | Unclear risk | "After baseline assessments, children randomly received either placebo or (...)" |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information |
| Blinding of participants and personnel (performance bias) | Unclear risk | Insufficient information |
| Blinding of outcome assessment (detection bias) | Unclear risk | No information |
| Incomplete outcome data (attrition bias) | Unclear risk | No information |
| Selective reporting (reporting bias) | Unclear risk | No protocol identified |
| Vested interest bias | High risk | Grants from Le Fonds de la Recherche en Santé du Québec and the Canadian Institutes of Health Research<br>Conflicts of interest: Yes. Dr. Joober is a principal investigator on a clinical trial not related to this study that is sponsored by AstraZeneca Canada Incorporated, and receives no direct compensation for this trial. Dr. Boivin has the following industry financial ties: The Litebook Company Ltd., Medicine Hat, Alberta, Canada; and Pulsar Informatics Inc., Vancouver, British Columbia, Canada |

## *Sharp 1999*

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| **Methods** | Cross-over trial with 3 interventions<br>1. Methylphenidate<br>2. Dextroamphetamine<br>3. Placebo<br>**Phases**<br>1. Three-week medical-free baseline, randomised administration of methylphenidate, dextroamphetamine and placebo followed by breakfast and lunch daily<br>2. Stepwise increase in stimulant dose each week<br>3. Each phase lasted 3 weeks<br>4. Dosage range: methylphenidate 10 mg/d to 70 mg/d, dextroamphetamine 5 mg/d to 30 mg/d |
| **Participants** | Number of participants screened: 150 (girls)<br>Number of participants included: 42 girls and 56 comparison boys<br>Number of participants followed up: 42<br>Number of withdrawals: 1 girl given placebo at each phase<br>Diagnosis of ADHD: DSM-IV (subtype not stated)<br>Mean age: 9.1 years (range 6.0 to 12.7)<br>Mean IQ: boys 109.3, girls 105.2<br>Sex: 56 boys, 42 girls<br>Methylphenidate naive: Elia 1991: 18 out of 48 had no previous stimulant drug treatment; Castellanos 1996: 80% had been previously treated with stimulants<br>Ethnicity: girls: Caucasian (67%), African American (19%), Hispanic (14%); boys: Caucasian (73%), African American (21%), Hispanic (4%), Asian (2%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: 71% boys, 69% girls; oppositional defiant disorder (33% boys, 50% girls), conduct disorder (7% boys, 2% girls), major depression (0% boys, 7% girls), separation anxiety (0% boys, 2% girls), specific phobias (0% boys, 7% girls), trichotillomania (2% boys, 0% girls), tic disorders not otherwise specified (13% boys, 2% girls), enuresis (18% boys, 12% girls), reading disorder (5% boys, 8% girls)<br>Comedication: not stated<br>Sociodemographics: SES mean score 48.0 ± 25.8 (girls), 52.4 ± 26.9 (boys)<br>**Inclusion criteria**<br>1. Girls with a history of severe hyperactivity, impulsivity and inattentiveness that interfered with home and school functioning<br>2. Symptoms of ADHD present in ≥ 2 settings<br>3. Conners' Hyperactivity factor scores from home teachers were ≥ 2 SD greater than age and sex norms<br>**Exclusion criteria**<br>1. Full-scale IQ < 80 on Wechsler Intelligence Scale for Children - Revised<br>2. Chronic medical or neurological disease, including Tourette's disorder and chronic tic disorders |

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| Interventions | Participants were randomly assigned to 1 of 6 possible drug condition orders of methylphenidate, dextroamphetamine and placebo<br>**Sharp 1999**<br>Mean methylphenidate dosage: week 1 mean dose 0.45 mg/kg, week 2 mean dose 0.85 mg/kg and week 3 mean dose 1.28 mg/kg<br>Administration schedule: breakfast and lunch - 5 days per week administered by nurse; administered by parent on weekends<br>**Elia 1991**<br>Mean methylphenidate dosage: week one 0.9 mg/kg, week two 1.5 mg/kg and week three 2.5 mg/kg<br>Administration schedule: 9:00 AM and 1:00 PM throughout the entire week (7 days)<br>Duration of each medication condition: 3 weeks<br>Washout before study initiation: 3-week medication-free period before study<br>Medication-free period between interventions: none<br>Titration period: none<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. Conners' Hyperactivity and Conduct factors score: teacher-rated<br>2. Wender Utah Rating Scale (WURS): parent-rated<br>3. Conners' Abbreviated Teacher Rating Scale (ABTRS): completed weekly<br>4. Conners' Teacher Rating Scale (CTRS): completed weekly<br>**General behaviour**<br>1. Child Behavior Checklist (CBCL): parent-rated<br>2. Woodstock-Johnson Achivement Battery: observer (psychologist)-rated<br>3. Teachers Report Form (TRF): teacher-rated<br>4. Conners' Parent Questionnaire (CPQ): completed weekly by parents<br>5. Children's Psychiatric Rating Scale (CPRS): completed weekly by psychiatric staff<br>6. Activity monitor (measuring truncal motor activity): from 9:00 AM to 4:00 PM<br>**Serious adverse events**<br>Mean beneficial and adverse effects of dextroamphetamine and methylphenidate were nearly identical for all ratings, including ratings of appetite problems. However, objectively verified significant decreases in body weight (drug main effect, F 10.27; P value = 0.0002) were significantly greater for dextroamphetamine (mean change -1.1 ± 1.0 kg from baseline; P value = 0.02) than for methylphenidate (-0.4 ± 1.1 kg; not significant)<br>Stimulant-related adverse effects and body weight<br>**Non-serious adverse events**<br>1. Subject Treatment Emergent Symptom Scale (STESS): physicians and parents<br>2. Some items on the CPRS, such as nervous mannerisms and obsessive thinking: rated as adverse effects (Elia 1991)<br>3. 24-hour urine and blood studies: at baseline and at third week for each treatment |

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| **Notes** | Sample calculation: no<br>Ethics approval: no information available<br>**Key conclusion of study authors**<br>1. Sharp 1999<br>a. Our primary conclusion is that our sample of girls demonstrated very similar patterns of comorbidity and impairment and identical patterns of drug response<br>**Comment from review authors**<br>1. We need a lot of information on the girls<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: no<br>Email correspondence with study authors: June 2014. We received supplemental information from Dr. Castellanos |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Order of medication (methylphenidate, placebo or dextroamphetamine) was randomly assigned on the basis of a table administered by the research pharmacy. Dose escalation was fixed, with 2 ranges, depending on body weight (> or < 30 kg). Three weeks (1 dose per week) in each phase. For most children, this was followed by random assignment to pemoline vs placebo after another washout period |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | Methylphenidate, dextroamphetamine and placebo were packaged in identical capsules by the NIH pharmacy and were administered by NH nurses in double-blinded randomly assigned order |
| Blinding of outcome assessment (detection bias) | Low risk | All ratings were performed blind to treatment assignment |
| Incomplete outcome data (attrition bias) | Unclear risk | Did not describe what they did with the missing data<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | No protocol published. All outcomes discussed were reported |
| Vested interest bias | Unclear risk | None mentioned<br>Conflicts of interest: not declared |

*Shiels 2009*

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| **Methods** | "3-day, double-blind, placebo-controlled medication assessment" |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 49<br>Number of participants randomly assigned: not stated<br>Number of participants followed up: not stated<br>Number of withdrawals: methylphenidate 0, placebo 0<br>Diagnosis of ADHD: DSM-IV (combined 35 (71%), hyperactive-impulsive 3 (6%), inattentive 11 (23%))<br>Age: mean 10.5 years (range 9 to 12)<br>IQ: mean 104 (range not stated)<br>Sex: 80% boys, 20% girls<br>Methylphenidate naive: not stated<br>Ethnicity: Caucasian (76%), African American (14%), other (10%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder (43%), conduct disorder (22%)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. DSM-IV ADHD diagnosis<br>2. Attending ADHD summer research programme<br>**Exclusion criteria**<br>1. Full-scale IQ < 80<br>2. History of seizures or other neurological problems or medication to prevent seizures<br>3. History of other medical problems for which psychostimulant treatment may involve considerable risk<br>4. Current use of psychotropic medications other than for ADHD (i.e. antipsychotics, mood stabilisers, antidepressants and anxiolytics)<br>5. History or concurrent diagnosis of pervasive developmental disorder, schizophrenia or other psychotic disorders<br>6. Absence of functional impairment<br>7. Vision or hearing problems that would make it difficult to complete discounting tasks (or other tasks; data not reported) |
| Interventions | Participants were assigned to extended-release methylphenidate in "high" or "low" dose (range 18 to 90 mg/d)<br>Mean methylphenidate: low dose 39 mg Concerta, high dose 73 mg Concerta<br>Administration schedule: once daily<br>Time points: in the morning, 90 minutes before cognitive task<br>Duration of intervention: 7:30 AM to 5:00 PM, Monday through Thursday<br>Titration period: not stated<br>Treatment compliance: not stated<br>Washout before study initiation: methylphenidate 1 week if taking atomoxetine, 24 hours if taking methylphenidate |
| Outcomes | **General behaviour**<br>Impairment Rating Scale (IRS; Fabiano 2006)<br>**Non-serious adverse events**<br>Pittsburgh Side Effects Rating Scale, blood pressure and heart rate assessed daily during times of peak medication effects |

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| **Notes** | Sample calculation: not stated<br>Ethics approval: not stated<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: none<br>**Key conclusions of study authors**<br>1. These findings provide initial evidence that stimulant medication reduces delayed discounting among those with the disorder<br>2. Methylphenidate, an effective pharmacological treatment for ADHD, reduced the preference for smaller immediate rewards over larger delayed rewards when delays and rewards were actually experienced by the child. This raises the possibility that stimulant medication improves real-world behaviour of children with ADHD by altering delay-related impulsivity<br>**Comment from review authors**<br>1. This study focused on effects of methylphenidate on "delay discounting", a function of impulsivity. However, no data are available on the effects of methylphenidate on ADHD symptoms more generally, nor are data available regarding side effects or changes in blood pressure and pulse.<br>Email correspondence with study authors: July 2014. Emailed study authors to request additional information but have not received a response |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not described |
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Blinding of participants and personnel (performance bias) | Low risk | "To maintain blinding, participants were given the same number of opaque capsules per day regardless of actual MPH dose" |
| Blinding of outcome assessment (detection bias) | Unclear risk | No information |
| Incomplete outcome data (attrition bias) | Unclear risk | Not described<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | Not described |
| Vested interest bias | High risk | Not described<br>Conflicts of interest: "In the past 3 years, James G. Waxmonsky has served on the Speakers Bureau for Novartis, received honoraria from Scepter, and received research support from Eli Lilly" |

### *Silva 2005a*

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| **Methods** | Six-week, randomised, single-blind, placebo-controlled, cross-over trial with 5 interventions<br>1. Extended-release methylphenidate 20 mg<br>2. Extended-release methylphenidate 40 mg<br>3. OROS methylphenidate 18 mg<br>4. OROS methylphenidate 36 mg<br>5. Placebo |

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| Participants | Number of participants screened: not stated<br>Number of participants included: 54 (34 boys, 20 girls)<br>Number of participants followed up: 53<br>Number of withdrawals: 1<br>Diagnosis of ADHD: DSM-IV (combined (70.4%), hyperactive-impulsive (1.9%), inattentive (27.8%))<br>Age: mean 9.4 years (range 6 to 12)<br>IQ: > 80<br>Methylphenidate naive: 0%<br>Ethnicity: Caucasian (63.0%), African American (14.8%), Asian (0%), other (22.2%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Children 6 to 12 years old<br>2. Meeting DSM-IV criteria for primary diagnosis of ADHD<br>3. Written consent from parents<br>4. Treated and stabilised on total daily dose of 20 mg to 40 mg methylphenidate for ≥ 2 weeks before enrolment<br>5. Females are required to be pre-menarchal, sexually abstinent or using an approved method of contraception<br>6. Females of childbearing potential are required to have a negative pregnancy test before enrolment<br>**Exclusion criteria**<br>1. IQ level ≤ 80<br>2. Diagnosed with Tourette's syndrome or a tic disorder<br>3. Deemed by investigator to be unable to comply with study instructions<br>4. Significant concurrent medical or psychiatric illness or substance abuse disorder<br>5. History of sensitivity to methylphenidate<br>6. History of substance abuse<br>7. Currently taking atomoxetine<br>8. Have taken, or is currently taking or planning to take, any investigational drug within 30 days of study start date |
| Interventions | Participants were randomly assigned to 1 of 10 possible drug condition orders of 20 mg extended-release methylphenidate, 40 mg extended-release methylphenidate, 18 mg OROS methylphenidate, 36 mg OROS methylphenidate and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: once<br>Duration of each medication condition: 1 day<br>Washout before study initiation: 1 day<br>Medication-free period between interventions: Participants were instructed to continue to take their regularly prescribed medication Sundays through Thursdays between study days; no medication was administered on Fridays to avoid possible carry-over effects during the Saturday treatment period<br>Titration period: none<br>Treatment compliance: not stated |

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| Outcomes | **ADHD symptoms**<br>1. Swanson, Kotkin, Agler, M-Flynn and Pelham Scale: by blinded raters, -0.5, 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 hours post dose. Primary analysis time point was 2 hours post dose<br>**Non-serious adverse events**<br>1. Adverse events were assessed throughout the classroom period day<br>Only 1 adverse event was considered to be drug-related |
| Notes | Sample calculation: yes; 46<br>Ethics approval: approved by an independent investigational review board<br>**Comments from study authors**<br>1. As available formulations of extended-release methylphenidate contain 11% more methylphenidate than their OROS methylphenidate counterparts, outcomes might appear to be biased toward extended-release methylphenidate<br>2. OROS methylphenidate releases a third bolus of active drug between 8 and 12 hours after dosing, whereas extended-release methylphenidate releases its last bolus at 4 hours post dose. Hence, outcomes during the last 4 hours of the day might, theoretically, be biased towards OROS methylphenidate<br>3. Study was conducted in a controlled laboratory classroom<br>4. These results are representative of participants who are known responders to methylphenidate<br>5. All participants had been previously stabilised on ADHD medication, so they may have been able to detect a difference between active treatment and placebo<br>**Key conclusions of study authors**<br>1. Efficacy of extended-release methylphenidate 20 mg is similar to that of OROS methylphenidate 18 mg and 36 mg during the first 8 hours post dose<br>2. Statistically greater benefits are observed with extended-release methylphenidate 40 mg than with OROS methylphenidate 36 mg and persist through hour 8<br>3. Active treatments show comparable efficacy from 8 to 12 hours post dose<br>4. Both doses of each methylphenidate formulation are well tolerated<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes<br>Email correspondence with study authors: April 2014. Sent an email to study authors to ask for additional data but have not receive a reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomised |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | All study personnel, with the exception of the nurse, pharmacist or physician dispensing medication, were blinded<br>Study medications were administered in an opaque container with a small aperture, so participants could not see them during administration |
| Blinding of outcome assessment (detection bias) | Low risk | The Swanson, Kotkin, Agler, M-Flynn and Pelham Scale was completed by blinded raters |
| Incomplete outcome data (attrition bias) | Unclear risk | No information<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | No protocol found |
| Vested interest bias | High risk | Funding from Novartis Pharmaceuticals Corporation<br>Conflicts of interest: All study authors have been consultants, have received honoraria or have worked for Novartis |

*Silva 2006*

| Methods | Cross-over trial with 2 interventions<br>1. D-MPH-ER 20 mg once daily<br>2. Placebo<br>Phases: 2 cross-over phases |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 54 (38 boys, 16 girls)<br>Number of participants followed up: 53<br>Number of withdrawals: 1<br>Diagnosis of ADHD: DSM-IV (combined (90.7%), hyperactive-impulsive (0%), inattentive (9.3%))<br>Age: mean 9.4 years (range 6 to 12)<br>IQ: not stated<br>Methylphenidate naive: none<br>Ethnicity: predominantly Caucasian<br>Country: USA<br>Setting: laboratory classroom<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Boys and girls<br>2. Age 6 to 12 years<br>3. Diagnosed with ADHD<br>4. Must have been stabilised on methylphenidate 20 mg/d to 40 mg/d for ≥ 1 month<br>5. For girls: pre-menarchal, sexually abstinent or using reliable contraceptive and have negative urine pregnancy test<br>**Exclusion criteria**<br>1. Investigator deemed IQ below average or evidence of IQ < 80; home-schooled<br>2. Tourette's syndrome<br>3. Tic disorder<br>4. Significant medical illness<br>5. Significant psychiatric illness (schizophrenia, bipolar disorder, autism)<br>6. Parents or guardians unable to understand or follow instructions<br>7. Taking antidepressants<br>8. Initiated psychotherapy 3 months before screening<br>9. Positive urine drug screening<br>10. Poor response to methylphenidate<br>11. Currently taking other medications for ADHD<br>12. Taking or planning to take another investigational drug within 30 days of study start; previously participated in d-MPH-ER study |
| Interventions | Participants were randomly assigned to 1 of 2 possible drug condition orders of 20 mg/d d-MPH-ER and placebo<br>Mean methylphenidate dosage: 20 mg/d<br>Administration schedule: once daily; morning<br>Duration of each medication condition: 1 week<br>Washout before study initiation: 1 day<br>Medication-free period between interventions: 1 day<br>Titration period: none<br>Treatment compliance: 100% in laboratory classroom sessions |
| Outcomes | **ADHD symptoms**<br>1. SKAMP: once weekly, observer-rated<br>**Non-serious adverse events**<br>1. Recorded adverse events described by parents and children, as well as in laboratory school setting, 1 day each week |

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| **Notes** | Sample calculation: yes<br>Ethics approval: not stated<br>**Comments from study authors**<br>1. One of the inclusion criteria in this study was that participants were known to be currently stable on another methylphenidate preparation<br>2. We listed all side effects, irrespective of whether they were reported by parent or child. These were gathered both during the week preceding laboratory observation days and during the laboratory classroom day<br>3. We did not systematically analyse compliance data during the week preceding the laboratory classroom<br>**Key conclusion of study authors**<br>1. In this study, once-daily d-MPH-ER 20 mg was a safe and effective treatment for paediatric participants with ADHD symptoms<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes<br>Any withdrawals due to adverse events: yes; 1 (during placebo)<br>Email correspondence with study authors: June 2014. Sent twice to study author to ask for additional information but have not received a reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Participants were randomly assigned by computerised random number assignment |
| Allocation concealment (selection bias) | Low risk | Study medication comprised 1 bottle of 5 capsules of blinded study medication or 1 bottle of 5 matching placebo capsules |
| Blinding of participants and personnel (performance bias) | Low risk | Double-blind. Study medication comprised 1 bottle of 5 capsules of blinded study medication or 1 bottle of 5 matching placebo capsules |
| Blinding of outcome assessment (detection bias) | Low risk | Three independent blinded raters |
| Incomplete outcome data (attrition bias) | Low risk | Safety population consisted of all participants who received ≥ 1 dose of study medication. Efficacy population comprised all randomly assigned participants who provided valid efficacy measurements for both treatment periods<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | No protocol identified |
| Vested interest bias | High risk | Financed by Novartis<br>Conflicts of interest: Some study authors have affiliations with medical companies |

*Silva 2008*

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| **Methods** | Randomised, multi-centre, double-blind, placebo-controlled, cross-over design with 2 interventions<br>1. d-MPH-ER<br>2. Placebo |

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| Participants | Number of participants screened: 68 (45 boys, 23 girls)<br>Number of participants included: 68<br>Number of participants followed up: 67<br>Number of withdrawals: 1 (from the placebo group)<br>Diagnosis of ADHD: DSM-IV (combined (82.4%), hyperactive-impulsive (0%), inattentive (17.6 %))<br>Age: mean 9.5 years (range 6 to 12)<br>IQ: > 70<br>Methylphenidate naive: none<br>Ethnicity: Caucasian (50%), African American (22.1%), Asian (0%), Hispanic (19.1%), other (8.8%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. 6 to 12 years of age<br>2. DSM-IV diagnosis of ADHD<br>3. Participants had to be clinically and behaviourally stable in the opinion of the referring physician and the site's principal investigator<br>4. Have taken their current dose of medication without adjustment for ≥ 2 weeks (this was required to be a total daily dose or nearest equivalent of methylphenidate 40 mg or immediate-release d-MPG 20 mg (Concerta 36 mg was allowed))<br>5. Parents and/or guardians had to provide informed consent<br>6. Female participants were required to be pre-menarcheal or sexually abstinent, or had to be using an adequate and reliable contraceptive method (e.g. double-barrier method), which was documented in the medical record. Girls who were sexually active were required to have a negative result on a urine pregnancy screening test<br>**Exclusion criteria**<br>1. Children were excluded if they or their parents/guardians were unable to understand or follow instructions necessary to participate in the study<br>2. If they were deemed by the investigator to have below-normal cognitive capacity, or if they were home schooled<br>3. Diagnosed with Tourette's disorder or a tic disorder, or had a history of, or concurrent, significant medical or psychiatric illness or substance abuse disorder<br>4. Children taking an antidepressant medication, those who initiated psychotherapy within the 3 months preceding screening and those with a positive urine drug screen<br>5. Also excluded were children with poor response or intolerance to methylphenidate, who were currently taking other medications for ADHD or were taking or planning to take any other investigational drug within 30 days of study start or who had previously participated in d-MPH-ER studies |
| Interventions | Participants were randomly assigned to d-ER-MPH or placebo<br>Mean methylphenidate dosage: 20 mg/d<br>Administration schedule: once daily, in the morning<br>Duration of each medication condition: 7 days<br>Washout before study initiation: 2 days<br>Titration period: none<br>Treatment compliance: not stated |

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| Outcomes | **ADHD symptoms**<br>1. Combined score on the Swanson, Kotkit, Agler, M-Flynn and Pelham Scale: measured at time points 1, 3, 4, 5, 7, 9, 10, 11 and 12 hours post dose by independent blinded raters. Rated at practice day (0), period 1 (visit day 7) and period 2 (visit day 14), and at final visit (visit day 15)<br>2. Attention and deportment scores on the Swanson, Kotkit, Agler, M-Flynn and Pelham Scale, obtained from 0.5 hours up to 12 hours by independent blinded raters. Rated at practice day (0), period 1 (visit day 7) and period 2 (visit day 14), and at final visit (visit day 15)<br>3. Combined score on the Swanson, Kotkit, Agler, M-Flynn and Pelham Scale, measured at time point 0.5 by independent raters. Rated at practice day (0), period 1 (visit day 7) and period 2 (visit day 14), and at final visit (15)<br>**Non-serious adverse events**<br>1. Vital signs obtained at practice day (0), period 1 (visit day 7) and period 2 (visit day 14), and at final visit (15)<br>2. Recording of spontaneously reported adverse events |
| Notes | Sample calculation: no<br>Ethics approval: yes<br>**Comment from study authors**<br>1. Unequal carry-over effects: As a result of the design used in this study, a test for carry-over effects could not be performed. Instead, tests of sequence effects in the analysis of the co-variance model were examined. If tests on sequence factors among time points were statistically significant (P value = 0.05), analyses were performed by each period<br>Limitations<br>1. Each participant took d-MPH-ER for only 1 week<br>2. Only 1 dose (20 mg/d) was used, meaning that results may not be generalisable to other doses<br>3. Study was confined to school-aged children, so applicability of results to pre-school children, adolescents or adults is unknown<br>4. All participants in this study had been previously shown to respond to and tolerate methylphenidate or D-MPH<br>5. Children who received placebo during the week before the laboratory classroom day showed statistically better pre-dose performance than children who received active medication on all measures except the Swanson, Kotkit, Agler, M-Flynn and Pelham Scale<br>**Key conclusions of study authors**<br>1. In this study, once-daily d-MPH-ER 20 mg was effective in treating both inattentive and behavioural symptoms in paediatric patients over a 12-hour laboratory classroom day<br>2. Primary efficacy variable - combined score on the Swanson, Kotkit, Agler, M-Flynn and Pelham Scale - showed significant superiority over placebo at all time points from 1 to 12 hours<br>3. Secondary efficacy variables indicated that onset of effect was rapid (0.5 hours) and duration of effect was relatively long (12 hours post dose)<br>4. In this sample, the drug was safe and well tolerated<br>5. Changes in vital signs were comparable with those of placebo<br>Inclusion of methylphenidate responders only/exclusion of MPH non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes<br>Email correspondence with study authors: October 2013. We received supplemental information from study authors regarding ethics approval and data. We were not able to obtain first period data |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Random assignment |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | All study medications were identical in appearance for blinding purposes; double-blind |
| Blinding of outcome assessment (detection bias) | Low risk | Double-blind |
| Incomplete outcome data (attrition bias) | Low risk | Safety population consisted of all participants who took ≥ 1 dose of study medication. Efficacy population included all randomly assigned participants who provided valid efficacy measurements for both treatment periods<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Low risk | Outcomes according to protocol |
| Vested interest bias | High risk | Funded by Novartis Pharmaceuticals Corporation<br>Conflicts of interest: Some study authors have affiliations with medical companies |

*Smith 1998*

| Methods | **Main study**<br>Eight-week intensive Summer Treatment Program, including a 6-week, double-blind, cross-over trial with 4 interventions<br>1. Three different doses of methylphenidate<br>2. Placebo<br>**Follow-up study**<br>Retrospective follow-up study of 16 individuals who completed double-blind, placebo-controlled, cross-over studies during 2 separate Summer Treatment Programs |
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| Participants | **Main study**<br>Number of participants screened: not stated<br>Number of participants included: 49<br>Number of participants followed up: 46 (41 boys, 5 girls)<br>Number of withdrawals: 3<br>Diagnosis of ADHD: DSM-III-R<br>Age: mean 13.8 years (range 12 to 17)<br>IQ: mean 101 (range 65 to 129)<br>Methylphenidate naive: 28%<br>Ethnicity: Caucasian (85%), African American (15%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder (50%), conduct disorder (15%)<br>Comedication: no<br>Sociodemographics: median family income US $38,500<br>**Inclusion criteria**<br>1. Meeting DSM-III-R diagnostic criteria for ADHD<br>2. 12th birthday before the protocol began<br>3. Verbal IQ > 80<br>4. No conditions that precluded a trial of stimulant medication or full participation in Summer Treatment Program academic and athletic activities<br>**Exclusion criteria**<br>1. No information<br>**Follow-up study**<br>Number of participants included: 16 (all boys)<br>Number of participants followed up: 16<br>Number of withdrawals: none<br>Diagnosis of ADHD: DSM-III-R<br>Age: mean (children) 10.2 years (range 8 to 11); mean (adolescents) 12.7 years (range 12 to 14.5)<br>IQ: mean (children) 109; mean (adolescents) 107<br>Methylphenidate naive: 4 (25%)<br>Ethnicity: Caucasian (100%)<br>Country: USA<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: family income (children US $37,943; adolescents US $49,650)<br>**Inclusion criteria**<br>1. Meeting DSM-III-R diagnostic criteria for ADHD<br>2. Younger than 12 years old when they participated in the children's Summer Treatment Program<br>3. Older than 12 years old when they participated in the adolescent Summer Treatment Program<br>4. Full-scale IQ > 80<br>5. No learning disabilities or physical condition that precluded full participation in Summer Treatment Program classroom activities, athletic activities or a trial of stimulant medication<br>**Exclusion criteria**<br>1. No information |

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| Interventions | **Main study**<br>Participants were randomly assigned to 1 of the possible drug condition orders of 25 mg/d, 50 mg/d or 75 mg/d methylphenidate and placebo<br>Mean methylphenidate dosage: 0.17 mg/kg<br>Administration schedule: 3 times a day: 7:45 AM, 11:45 AM, 3:45 PM<br>Duration of each medication condition: 6 days<br>Washout before study initiation: 2 weeks<br>Medication-free period between interventions: 16 hours<br>Titration period: none<br>Treatment compliance: not stated<br>**Follow-up study**<br>Participants were randomly assigned to 1 of the possible drug condition orders of 0.3 mg/kg methylphenidate and placebo<br>Mean methylphenidate dosage: 0.3 mg/kg<br>Administration schedule: twice a day: 8:00 AM and 12:00 PM<br>Duration of each medication condition: 1 day<br>Washout before study initiation: 2 weeks<br>Medication-free period between interventions: 20 hours<br>Titration period: none<br>Treatment compliance: not stated. Adolescents were evaluated on a protocol that included placebo and 3 doses of methylphenidate. To facilitate comparison, doses for adolescents were converted to milligrams per kilogram, and the dose closest to 0.3 mg/kg was used in this study |
| Outcomes | **ADHD symptoms**<br>1. IOWA Conners' Rating Scale (subscale: Inattention/Overactivity): completed every day by counsellors and classroom teachers<br>**General behaviour**<br>1. IOWA Conners' Rating Scale (subscale: Oppositional Defiant): completed every day by counsellors and classroom teachers<br>**Non-serious adverse events**<br>1. Smith 1998: Side effects rating form (rating 12 potential side effects associated with stimulant medication on a 4-point scale. A side effect rating of 3 (severe) was defined as troubling enough to contraindicate that dose of medication): completed every day by counsellors and parents during medication assessment<br>2. Evans 1997: Ratings on major side effects associated with MPH: completed each day by classroom teachers |

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| Notes | Sample calculation: no<br>Ethics approval: not stated<br>**Comments from study authors**<br>Main study<br>1. One participant had a full-scale IQ of 65 but was judged to be sufficiently intelligent to understand the behavioural contingencies, activity rules and social skills training provided in the programme<br>2. Comment on high response rate in this study compared with other studies of adolescents with ADHD<br>a. Higher response rate in this study may be due to greater statistical and methodological power to detect medication effects compared with previous studies, including (1) a larger sample, (2) a broader range of doses, (3) measurement in a well-controlled, naturalistic setting, (4) repeated replications of medication conditions and (5) a statistical cutoff of 0.5 to define a positive response to medication<br>Follow-up study<br>1. For data compared in this study, randomisation and medication administration procedures were identical for children and adolescents, except that adolescents were evaluated on a protocol that included placebo and 3 doses of methylphenidate. To facilitate comparison, doses for adolescents were converted to milligrams per kilogram, and the dose closest to 0.3 mg/kg was used in this study<br>2. Sample included only Caucasian males<br>3. Only one third of participants in the adolescent programme had completed the summer treatment programme for children<br>4. Students exhibited a much higher than expected positive response to stimulant medication<br>**Key conclusions of study authors**<br>Main study<br>1. Results show that the shape of the dose-response curve is influenced by the measurement method; most adolescents exhibited improved social behaviour when treated with methylphenidate, most positive effects of methylphenidate were achieved at the lowest dose and diminishing positive effects and increasing risk of negative effects were noted with successively higher doses<br>Follow-up study<br>1. Stimulant medication is equally effective with children and adolescents with ADHD who are engaged in similar activities<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: no<br>Email correspondence with study authors: September 2014. We contacted study authors twice to ask for supplemental information/data but have received no response |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Medication conditions were randomly assigned daily, with each condition occurring once a week. Thus, adolescents received a mode of 6 replications of each medication condition |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Unclear risk | Double-blind; no further information |
| Blinding of outcome assessment (detection bias) | Unclear risk | Double-blind; no further information |
| Incomplete outcome data (attrition bias) | Unclear risk | "Some missing data was caused by holidays or absences from the program"<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | No protocol |
| Vested interest bias | Low risk | Supported by grants from the National Institute on Drug Abuse, the National Institute of Mental Health, the National Institute on Alcohol Abuse and Alcoholism and the National Institute of Child Health and Human Development<br>Conflicts of interest: not declared |

*Smith 2004*

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| **Methods** | n-of-1 randomised, double-blind, cross-over trial investigating the effects of Ritalin on the disruptive behaviour of a child diagnosed with ADHD. One-day antecedent analysis in the clinic followed by an extended school-based trial, during which participants received methylphenidate or placebo before evaluation<br>Duration: 15 days |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 1 boy<br>Number of participants followed up: 1<br>Number of withdrawals: none<br>Diagnosis of ADHD: DSM-IV (subtype: not stated)<br>Age: 11 years<br>IQ: 124<br>Methylphenidate naive: no<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Not stated<br>**Exclusion criteria**<br>1. Not stated |

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| Interventions | Participant was randomly assigned to 1 of 2 possible drug condition orders of (20 mg/d) immediate-release methylphenidate and placebo.<br>Out-patient clinic setting, duration 1 day: ingestion of 20 mg methylphenidate or placebo 45 minutes before evaluation (randomised)<br>Cross-over 4 hours later followed by second evaluation<br>School setting: 15 days (3 school weeks)<br>Administration schedule: once daily, mornings, 45 minutes before first evaluation<br>Medication-free periods: on weekends; a total of 9 days with medication and 6 days without, randomly assigned throughout the trial period<br>Titration period: no<br>Washout period before study initiation: none other than weekends<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. ADHD Rating Scale, Fourth Edition - School Version (18 items): completed by the teacher and an independent observer in the classroom. Classroom assessments were conducted within normal classroom activities in the morning (first 4 hours of school). Mean inter-rater reliability 79% (range 56% to 100%) |
| Notes | Sample calculation: no<br>Ethics approval: *n*ot stated<br>**Comments from study authors**<br>1. A major problem with single data point analyses is the difficulty involved in generalising outcomes to other settings and times<br>2. Another difficulty involved inclusion of only 1 participant. However, the objectivity of clinic data in combination with checklist outcomes provides generalisable results, which reduces some of these limitations<br>**Key conclusion of study authors**<br>1. The investigation suggests that the 1-day antecedent analysis procedure could be used as an initial evaluation of the use of Ritalin<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: October 2013. We received from study authors supplemental information regarding diagnostic criteria |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | A third party, who was not involved in the clinical procedure, determined the selection of actual medication packs |
| Allocation concealment (selection bias) | Low risk | A third party, who was not involved in the clinical procedure, determined the selection of actual medication packs |
| Blinding of participants and personnel (performance bias) | Unclear risk | A third party, not involved in the clinical procedures, determined the selection of actual medication packs. Thus, persons conducting the direct evaluation were blinded to all medication manipulations (i.e. the child, parents, therapists and data collectors). However, no description was provided about whether medication and placebo pills were identical. "Prior to clinical assessment, two packets of medication were provided to the participant's parent. One package contained 20 mg of Ritalin and the other package contained a placebo" |
| Blinding of outcome assessment (detection bias) | Low risk | A third party, who was not involved in the clinical procedure, determined the selection of actual medication packs. Thus, persons conducting the direct evaluation were blinded to all medication manipulations (i.e. the child, parents, therapists and data collectors) |
| Incomplete outcome data (attrition bias) | Low risk | No<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | No protocol identified and no email from study author |
| Vested interest bias | Unclear risk | Not stated |

### *Smithee 1998*

| Methods | Cross-over trial with 2 interventions<br>1. Methylphenidate<br>2. Placebo |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 26 (20 boys, 6 girls)<br>Number of participants followed up: not stated<br>Number of withdrawals: not stated<br>Diagnosis of ADHD: DSM-IV (combined (77% ), inattentive (23%))<br>Age: mean 9.63 years (range 6.5 to 12)<br>IQ: mean 99.71<br>Methylphenidate naive: 24<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant/conduct disorder (n = 13a), anxiety disorders (n = 13), nocturnal enuresis (n = 4), vocal tics (n = 4), motor tics (n = 3)<br>Comedication: not stated<br>Sociodemographics: middle class status; mean social class of 2.12<br>**Inclusion criteria**<br>1. 6.5 to 12 years of age<br>2. Full-scale, verbal or performance IQ ≧ 85<br>3. Normal or corrected vision and hearing<br>4. No physical handicaps<br>5. No history of psychotic or neurological disorder<br>6. No previous psychotropic treatment except for brief interventions of at most a couple of months (n = 2)<br>**Exclusion criteria**<br>1. None stated |
| Interventions | Participants were randomly assigned to 1 of 2 possible drug condition orders of methylphenidate and placebo<br>Mean methylphenidate dosage: 0.78 mg/kg/d<br>Administration schedule: 3 times daily for 14 days per medication conditions<br>Time points: morning, noon and 4:00 PM<br>Duration of each medication condition: 14 days<br>Washout before study initiation: not stated<br>Medication-free period between interventions: no<br>Titration period: on days 1 to 3, participants received a dose 2.5 mg below their target dose of 0.3 mg/kg b.i.d. On days 4 to 7, dose was raised to 0.3 mg/kg b.i.d., and on day 8, the 4:00 PM dose was added<br>Treatment compliance: not stated |

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| Outcomes | **ADHD symptoms**<br>1. Abbreviated Conners' Hyperactivity Questionnaire, parent and teacher: before trial and at each phase of 14 days<br>2. IOWA, parent and teacher: before trial and at each phase of 14 days<br>3. Hyperactivity Attention and Aggression Scales of the TOTS, parent and teacher: before trial and at each phase of 14 days<br>**Non-serious adverse events**<br>1. Weight with clothes but without shoes: observer, before and last day of each phase<br>2. Interview to assess the presence of side effects: 11 somatic side effects and 3 mood problems<br>3. Appetite decrease, increased thirst, dry mouth, stomachaches, nausea, headaches, dizziness, tremors, drowsiness, sleep problems, tics, crying, anger and sadness, EEG<br>Relatively few side effects were reported, probably in part because of adjustment in dosages in response to emergent symptoms |
| Notes | Sample calculation: no<br>Ethics approval: not stated<br>**Comment from study authors**<br>1. Teachers tended to detect greater improvement with medication than did parents. Nevertheless, both parents and teachers detected significant improvement with treatment<br>**Key conclusion of study authors**<br>1. Stimulant treatment increased accuracy and speed among younger children and curtailed variability of reaction time for the sample as a whole. However, methylphenidate did not affect ERPs. In combination, results imply that enhancement of performance by methylphenidate does not involve the demands of response selection examined in this trial<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with trial authors: March 2014. We received supplemental data from trial authors |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Medications were administered in random order |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Low risk | Medications were administered in random order, under double-blind conditions; capsules of identical appearance and taste |
| Blinding of outcome assessment (detection bias) | Low risk | At the end of each phase, an investigator blind to pharmacological conditions administered a structured interview to the child's parent concerning emergent side effects in the preceding period |
| Incomplete outcome data (attrition bias) | Unclear risk | Reports of side effects led to bind reduction of dosages or omission of planned increments for 3 participants under methylphenidate<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | Table with numbers of reported somatic effects not given |
| Vested interest bias | Low risk | Research supported by National Institute of Mental Health (NIMH) Grant MH 38228; Rafael Klorman<br>Conflicts of interest: not declared |

*Solanto 2009*

| Methods | Cross-over trial with 2 interventions<br>1. Methylphenidate<br>2. Placebo<br>Phases: week-long exposure to placebo and to each of 3 different dosage regimens of immediate-release methylphenidate |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 30<br>Number of participants followed up: 25<br>Number of withdrawals: 5<br>Diagnosis of ADHD: DSM-IV (combined (60%), inattentive (40%))<br>Age: not stated<br>IQ: not stated<br>Sex: not stated<br>Methylphenidate naive: All but 1 were stimulant-naive<br>Ethnicity: not stated<br>Country: USA<br>Setting: hospital<br>Comorbidity: oppositional defiant disorder (combined 13%, predominantly inattentive 20%); learning disability (combined 40%, predominantly inattentive 20%); anxiety (combined 0%, predominantly inattentive 10%)<br>Comedication: no<br>Sociodemographics: minority representation (combined 53%, predominantly inattentive 20%)<br>**Inclusion criteria**<br>1. Between 7 and 12 years of age<br>2. Concordant reports: Conners' Parent Rating Scale and Conners' Teacher Rating Scale - Combined group T scores ≧ 65 on both DSM-IV Inattentive and DSM-IV Hyperactive-Impulsive Scales<br>3. Predominantly Inattentive group T scores ≧ 65 on the DSM-IV Inattentive Scale and < 65 on the DSM-IV Hyperactive-Impulsive scale<br>4. Diagnosis of ADHD, combined or predominantly inattentive according to a structured diagnostic interview of the parent: Diagnostic Interview Schedule for Children and Adolescents<br>5. Expert clinical diagnosis of ADHD based on review of all information collected<br>**Exclusion criteria**<br>1. Currently receiving psychotropic medication<br>2. Wechsler Intelligence Scale for Children, Third Edition: < 80<br>3. Mood disorder, Tourette's disorder or psychotic disorder<br>4. Sensory impairment or chronic medical or neurological condition including asthma that required systemic medication<br>5. Colour blindness |
| Interventions | Participants were randomly assigned to 1 of 24 possible drug condition orders of low-dose, medium-dose and high-dose methylphenidate and placebo<br>Mean methylphenidate dosage (Combined vs predominantly Inattentive): low dose 0.50 ± 0.12 vs 0.44 ± 0.13; medium dose 0.83 ± 0.20 vs 0.73 ±-0.21; high dose 1.54 ± 0.31 vs 1.40 ± 0.38<br>Administration schedule: 3 times daily: morning, midday and 3:00 PM<br>Duration of each medication condition: 1 week<br>Washout before study initiation: not required<br>Medication-free period between interventions: no<br>Titration period: open-label lead-in week, not specified whether before or after randomisation of treatment<br>Treatment compliance: not stated |

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| Outcomes | **ADHD symptoms**<br>1. Conners' Parent Rating Scale, parent and teacher: baseline and end of each medication phase<br>2. Conners' Teacher Rating Scale, parent and teacher: baseline and end of each medication phase<br>3. ADHD Rating Scale, Fourth Edition: observer, weekly<br>**Non-serious adverse events**<br>1. Height, weight and vital signs: observer, weekly<br>2. Side Effects Rating Scale: observer, weekly |
| Notes | Sample calculation: no<br>Ethics approval: not stated<br>**Key conclusion of study authors**<br>1. Results support the clinical utility of methylphenidate in the treatment of predominantly inattentive subtype and provide no evidence of differences in response between subtypes<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: April 2014. We received supplemental information from study authors |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not stated |
| Allocation concealment (selection bias) | Low risk | Double-blind, cross-over with week-long exposure to placebo and each of 3 different dosage regimens of immediate-release methylphenidate in randomly assigned order |
| Blinding of participants and personnel (performance bias) | Low risk | Double-blind, cross-over with week-long exposure to placebo and each of 3 different dosage regimens of immediate-release methylphenidate in randomly assigned order. Study medications were prepared and coded by the hospital pharmacy using identical gelatin capsules for active medication and placebo |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not stated |
| Incomplete outcome data (attrition bias) | Low risk | Across the 4 placebo and drug conditions, data points were missing as follows: Parent Conners' 1%, Teacher Conners' 6%, Parent SKAMP 1%, Teacher SKAMP 4%, Side Effects 0%. Missing scores were replaced by the mean of scores for that group in that condition<br>Selection bias: titration conducted but unclear whether before or after randomisation. No participants were excluded after the 1-week titration period |
| Selective reporting (reporting bias) | Low risk | Protocol identified; all outcomes reported |
| Vested interest bias | High risk | No information<br>Conflicts of interest: Three study authors have served or received grants from pharmaceutical companies in the past |

***Stein 1996***

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| **Methods** | Five-week, triple-blind, placebo-controlled, cross-over trial with 4 interventions<br>1. Methylphenidate twice daily<br>2. Methylphenidate 3 times daily<br>3. Methylphenidate titration<br>4. Placebo |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 25 (all boys)<br>Number of participants followed up: 24<br>Number of withdrawals: 1<br>Diagnosis of ADHD: DSM-III-R (combined (88%), inattentive (12 %))<br>Age: mean 8.0 years (range 6 to 12)<br>IQ: not stated<br>Methylphenidate naive: 44%<br>Ethnicity: Caucasian (96%), Hispanic (4%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder (28%), conduct disorder (12%)<br>Comedication: no<br>Sociodemographics: Hollingshead SES category I: 8 (33%), II: 8 (33%), III: 3 (12.5%), IV: 5 (20.8%)<br>**Inclusion criteria**<br>1. DSM-III-R ADHD diagnosis from parent interview using Disruptive Behavior Disorders module of the NIMH Diagnostic Interview Schedule for Children - Parent-rated (DISC-P)<br>2. Clinically significant ratings on Conners' Parent Rating Scale for Impulsivity/Hyperactivity factor (T > 65) or on Child Behavior Checklist (parent form)<br>3. Attention factor (T > 65)<br>4. Teacher ratings below 20th percentile for attention or hyperactivity problems on the ADD-H Teacher Rating Scale (ACTeRS)<br>**Exclusion criteria**<br>1. History of significant developmental delay (indicated by IQ testing or special educational services)<br>2. Diagnosis of pervasive developmental disorder<br>3. Unwillingness of parents or school personnel to meet study requirements |
| **Interventions** | Participants were randomly assigned to 1 of 4 possible drug condition orders of methylphenidate and placebo<br>Mean methylphenidate dosage: 8.8 mg, 0.3 mg/kg/dose<br>Administration schedule: twice/3 times daily: 8:00 AM, 12:00 PM (and 2:00 PM)<br>Duration of each medication condition: 1 week<br>Washout before study initiation: ≥ 5 days<br>Medication-free period between interventions: none<br>Titration period: initiated after randomisation<br>Treatment compliance: "there was generally good compliance, with a mean of 1.5 missed doses per child over the 5-week course of the study" |

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| Outcomes | **ADHD symptoms**<br>1. Conners' Parent Rating Scale (CPRS), 48 items; factors include Conduct Problem, Learning Problem, Psychosomatic Problems, Impulsivity/Hyperactivity and Anxiety. Collected on a weekly basis for 5 consecutive weeks, including baseline assessment<br>2. ADD-H Comprehensive Teacher Rating Scale (ACTeRS): collected on a weekly basis for 5 consecutive weeks, including baseline assessment<br>**Serious adverse events**<br>1. None observed<br>**Non-serious adverse events**<br>1. Stimulant Side Effects Rating Scale (SSERS): collected on a weekly basis for 5 consecutive weeks, including baseline assessment<br>2. Sleep log: Parents completed a sleep log to record the time when the child was sent to bed and fell asleep, as well as total sleep duration<br>3. Actigraph: For 2 consecutive 18-hour periods during each week, children wore an actigraph wrist monitor from 4:00 PM to 8:00 AM to record activity level, latency to sleep onset (time sent to bed to first minute of sleep), duration of sleep and number and duration of awakenings |
| Notes | Sample calculation: no<br>Ethics approval: approved by the Institutional Review Board of the University of Chicago<br>**Comments from study authors**<br>1. Analysis revealed no significant effects of order on any of the measures of ADHD symptoms, sleep variables and side effects<br>2. Our sample size and resultant statistical power were moderate, limiting our ability to detect mild or subtle effects<br>**Key conclusions of study authors**<br>1. For many children with ADHD, t.i.d. dosing may be optimal<br>2. Few differences in acute side effects have been noted between b.i.d. and t.i.d. methylphenidate dosing<br>3. Dosing schedule should be selected according to severity and time course of ADHD symptoms, rather than in anticipation of dosing schedule-related side effects<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: July 2014. Supplemental information regarding randomisation and whether all planned outcomes were measured and reported was received from study authors. Unfortunately, study authors no longer had access to the dataset; therefore it has not been possible to receive supplemental data |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Participants were randomly assigned to 1 of 4 different orders of drug administration. The research pharmacist used a random numbers table to assign participants to different orders of administration |
| Allocation concealment (selection bias) | Low risk | "All medication and placebos were prepared by the study pharmacist and placed in opaque gelatin capsules" In addition to the pharmacist, 1 investigator had access to the dosage code in the event of a medical emergency that necessitated breaking the blind |
| Blinding of participants and personnel (performance bias) | Low risk | Triple-blinded: Participants always took 3 capsules daily during the study. "Active drug phase (b.i.d. or three t.i.d.) was always preceded by a titration phase. The purpose of the titration phase was to introduce a typical dose of MPH gradually, so that any observation of side effects during the b.i.d. and t.i.d. dosing phases could not be attributed to rapid introduction of MPH"; "All medication and placebos were prepared by the study pharmacist and placed in opaque gelatin capsules"; "In addition to the pharmacist, one investigator had access to the dosage code in the event of a medical emergency that necessitated breaking the blind" |
| Blinding of outcome assessment (detection bias) | Low risk | Triple-blinded: In addition to the pharmacist, one investigator had access to the dosage code in the event of a medical emergency that necessitated breaking the blinding |
| Incomplete outcome data (attrition bias) | Low risk | One drop-out. Data collected on this participant were used in the descriptive information for baseline, t.i.d. and titration phases<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Low risk | All planned outcomes were measured and reported |
| Vested interest bias | Low risk | None declared. The work was supported by the Smart Family Foundation<br>Conflicts of interest: no affiliations with pharmaceutical companies stated |

*Stein 2003*

| Methods | Four-week, double-blind, placebo-controlled, cross-over trial in which participants were randomly assigned to<br>1. Three doses of methylphenidate<br>2. Placebo |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 47 (33 boys, 14 girls)<br>Number of participants followed up: 39<br>Number of withdrawals: 8<br>Diagnosis of ADHD: DSM-IV (combined (68%), hyperactive-impulsive (0%), inattentive (32%))<br>Age: mean 9.02 years (range 5 years 11 months to 16 years)<br>IQ: mean 106.8<br>Stimulant-naive: 70%<br>Ethnicity: Caucasian (89.4%), African American (4.3%), Hispanic (2.1%), other (4.3%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder (17%), encopresis/enuresis (10.6%), tic disorder (2.1%)<br>Comedication: no<br>Sociodemographics: predominantly mid to upper socioeconomic status referral base of the clinic<br>**Inclusion criteria**<br>1. DSM-IV criteria for ADHD<br>**Exclusion criteria**:<br>1. Mental retardation<br>2. Severe mood disorders (requiring antidepressant or concurrent psychotropic medications)<br>3. Tourette's syndrome, seizure disorders or other medical disorders associated with symptoms that may mimic ADHD (e.g. thyroid disorder)<br>4. Children taking systemic medications |
| Interventions | Participants were randomly assigned to different orders of OROS methylphenidate (18 mg, 36 mg, 54 mg) and placebo. No child could start with the 54-mg dose, and 1 child who weighed < 40 kg did not receive the 54-mg dose to minimise potential side effects in smaller children<br>Administration schedule: once daily<br>Duration of each medication condition: 7 days<br>Washout before study initiation: 2-week washout period for children who took stimulant medication before study start<br>Medication-free period between interventions: no<br>Titration period: none<br>Treatment compliance: 92% of all study medications were given |
| Outcomes | **ADHD symptoms**<br>1. ADHD Rating Scale, Fourth Edition: parent-rated, at baseline and weekly during interventions<br>2. ACTeRS: teacher-rated at baseline and weekly during interventions<br>**Non-serious adverse events**<br>1. Side Effect Rating Scale (SERS; Barkley 1990): parent-rated at baseline and weekly during interventions<br>2. Vital signs (weight, height, blood pressure, pulse and temperature): obtained weekly by clinical staff<br>3. Children’s Sleep Questionnaire |

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| Notes | Sample calculation: no<br><br>Ethics approval: approved by the Institutional Review Boards of The University of Chicago, Children's National Medical Center and the General Clinical Research Center Advisory Council<br><br>**Comments from study authors**<br><br>1. Forced titration procedure deserves some comment<br>2. The advantage of this procedure is increased potential to determine optimal response. However, this procedure is likely to result in increased reports of stimulant side effects compared with a more gradual titration procedure<br><br>In interpreting the results, several limitations should be kept in mind<br><br>1. Potential expectancy biases or placebo effects need to be considered because each medication differed in appearance, size and colour, and, in the case of the 54-mg condition, number of capsules<br>2. Other limitations include the short-term nature of the study, the relatively small number of participants with ADHD predominantly inattentive subtype and the measures of ADHD symptoms used that were rating scales rather than behavioural observations or laboratory measures of attention<br><br>**Key conclusions of study authors**<br><br>1. In children with ADHD combined subtype - the most common subtype of ADHD - increasing doses of stimulant medication were associated with increased improvement in inattention and hyperactivity symptoms<br>2. In children with ADHD predominantly inattentive subtype, symptom improvement occurred at lower doses and less benefit was derived from higher doses<br>3. In both ADHD subtypes, higher doses were associated with parent ratings of increased insomnia and decreased appetite<br>4. Children who were homozygous for the less common, 9-repeat DAT1 30-UTR genotype displayed a distinct dose–response curve from that of other genotype groups, with absence of typical linear improvement when the dose was increased from 18 mg to 36 mg and 54 mg<br><br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br><br>Correspondence with study authors: August 2014. We contacted study authors to request additional data. Study authors no longer have access to the data |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Dosing schedules were assigned from a randomly ordered list of all dosing schedules |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | High risk | Each medication differed in appearance, size and colour and, in the case of the 54-mg condition, number of capsules. The placebo capsule was slightly larger than the methylphenidate preparations. Study authors conducted several analyses to investigate the impact of these differences in appearance on the findings of the study (almost no impact on the results) but still considered risk of bias to be high. Parents and clinicians who were blinded to genotype and medication status rated ADHD symptoms, impairment and stimulant side effects each week |
| Blinding of outcome assessment (detection bias) | Low risk | Parents and clinicians who were blinded to genotype and medication status rated ADHD symptoms, impairment and stimulant side effects each week |
| Incomplete outcome data (attrition bias) | Unclear risk | Any child who could not complete a treatment phase was classified as a premature discontinuation. Their data were included for all phases that were completed. No description on how many participants the analyses were based on |
| Selective reporting (reporting bias) | High risk | Data were included for all phases that were completed. There is no description that reveals how many people the analyses were based on. In the abstract belonging to the study (Stein et al. 2004), researchers write that they will "prospectively evaluate the effects of different doses of stimulant medication on these and other sleep problems". This is not provided in any of the articles included in the Stein 2003 study |
| Vested interest bias | High risk | This study was supported by the National Institute of Mental Health, the General Clinical Research Center Program of the National Center for Research Resources and the National Institutes of Health, Department of Health and Human Services<br>Conflicts of interest: Drs. Stein, Robb, Conlon and Newcorn participate in the Speakers' Bureau for McNeil Consumer and Specialty Pharmaceuticals, and Drs. Stein and Newcorn are members of the Concerta National Advisory Committee |

*Stein 2011*

| Methods | Eight-week, double-blind, cross-over trial comparing the following<br>1. Extended-release d-MPH (10 mg, 20 mg, 25 to 30 mg)<br>2. Extended-release MAS (10 mg ,20 mg, 25 to 30 mg)<br>with a week of randomly assigned placebo within each drug period |
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| Participants | Number of participants screened: 77<br>Number of participants included: 65<br>Number of participants followed up: 56<br>Number of withdrawals: 9<br>**Demographic data on the 56 participants**<br>Diagnosis of ADHD: DSM-IV (combined (67%), hyperactive-impulsive (0%), inattentive (33%))<br>Age: mean 11.78 years (range 9 to 17)<br>IQ: > 70<br>Sex: 41 boys, 15 girls<br>MPH-naive: 35.7%<br>Ethnicity: Caucasian (41.0%), African American (41.0%), Asian (2%), Hispanic (7%), Bi-racial/mixed (9%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. DSM-IV diagnosis of ADHD, any subtype<br>2. Signed informed consent and assent<br>3. Clincal Global Impressions - Severity for ADHD (CGI-S-ADHD) rating ≥ 4<br>4. Findings on physical exam, laboratory studies, vital signs and ECG are judged to be normal for age<br>5. Pulse and blood pressure are within 95% of age and sex means<br>6. Able to complete study instruments and swallow capsules<br>7. Willing to commit to the entire visit schedule for the study, including ≥ 1 visit to UIC Medical Center<br>**Exclusion criteria**<br>1. Mental retardation, autism, severe mood disorders, Tourette's disorder, seizure disorders or other medical disorders that were contraindications of stimulant treatment that mimic ADHD (e.g. thyroid disorder)<br>2. Non-responder to either medication at doses offered in the study in an adequate trial. Must not have experienced disabling adverse effects with either medication<br>3. Concomitant psychotropic medications or medications that might have a CNS effect are required<br>4. Any other medical condition that represents a contraindication for either treatment<br>5. History of alcohol or drug abuse in the past 3 months, or a positive urinary toxic screen on initial evaluation that is not explained by a time-limited medical circumstance<br>6. Females of childbearing age who are sexually active, do not use acceptable birth control (double protection method) and, after counselling, are unwilling to do so<br>7. History of allergic reactions to multiple medications<br>8. History of psychosis<br>9. Diagnosis of bipolar disorder |

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| Interventions | Participants were randomly assigned to 3 dose conditions of ER d-MPH and ER MAS administered sequentially from lowest to highest dose with a randomly assigned week of placebo during each period<br><br>Methylphenidate dosage: 10 mg, 20 mg and 25 to 30 mg. Maximum dose was 25 mg in smaller children (i.e. < 35 kg) to minimise potential side effects<br><br>Administration schedule: once daily<br><br>Duration of each medication condition: 1 week<br><br>Washout before study initiation: 2-day washout period before beginning of the trial. No washout period between treatment periods<br><br>Titration period: none<br><br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br><br>1. ADHD Parent Rating Scale, Fourth Edition, rated weekly<br><br>**Non-serious adverse events**<br><br>1. Stimulant Side Effects Rating Scale (Barkley 1990): rated weekly by parents<br>2. Vital signs (weight, height, blood pressure, pulse and temperature): obtained weekly<br>3. ECG before and after study<br>4. Sleep measured by actigraphy and questionnaires (from abstract) |
| Notes | Sample calculation: no<br><br>Ethics approval: approved by the Institutional Review Board of University of Illinois at Chicago<br><br>**Comment from study authors**<br><br>1. Short duration of time children were maintained on each dose and fixed dose titration<br><br>**Key conclusions of study authors**<br><br>1. Both ER d-MPH and ER MAS were associated with significant, dose-dependent reductions in ADHD symptoms<br>2. Decreased appetite and insomnia were more common and were seen at higher dose levels for both stimulants<br>3. Dose level, rather than stimulant class, was strongly related to medication response<br>4. Although most children responded similarly to both stimulants, 14.3% of total samples were responders to ER d-MPH only, and 12.5% responded only to ER MAS<br>5. Future comparative effectiveness studies with multiple informants and larger samples over longer time periods are necessary to develop a data-driven, personalised approach to ADHD treatment<br><br>**Comment from review authors**<br><br>1. Protocol states that an exclusion criterion was "Non-responder to either medication at the doses offered in the study in an adequate trial". This is not written in the full text of the study. Asked study author about this issue, who replied, "Although non response was an exclusion [criterion] a priori, in fact this did not come up and no cases were excluded from participation based upon this". Even though this means that children in the trial were not only responders, we still choose to analyse this study as part of the studies that included only responders<br><br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; see comments above<br><br>Email correspondence with study authors: November and December 2013. We received supplemental data from study authors |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Order of drug was randomly assigned so that 50% started with ER d-MPH and 50% started with ER MAS; also a randomly assigned week of placebo during each period |
| Allocation concealment (selection bias) | Low risk | Weekly blister packs containing capsules of study drug, which were indistinguishable from each other |
| Blinding of participants and personnel (performance bias) | Low risk | Participant, caregivers, outcome assessors |
| Blinding of outcome assessment (detection bias) | Low risk | Participant, caregivers, outcome assessors |
| Incomplete outcome data (attrition bias) | Low risk | All study participants who received ≥ 2 weeks of study drug to ensure that all participants had been exposed to ≥ 1 week of active drug were analysed<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Low risk | No. Regarding the Wiebe et al. abstract, a paper is almost ready for submission |
| Vested interest bias | High risk | Investigator-initiated study sponsored by Novartis Pharmaceuticals, with additional support provided by the University of Illinois at Chicago (UIC) Center for Clinical and Translational Science (CCTS)<br>Conflicts of interest: Some study authors are affiliated with pharmaceutical companies |

*Stoner 1994*

| Methods | Two n-of-1, double-blind, placebo-controlled, cross-over, randomised controlled trial. Both cases received 4 levels of the following<br>1. Methylphenidate 5 mg, 10 mg and 15 mg<br>2. Placebo<br>After the double-blind trial, the code was broken, and the best dose was administered to the participant. Follow-up data on the best dose were also measured. Follow-up data were recorded anecdotally for the first case (Dan) and systematically for the second case (Bill) |
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| Participants | Number of participants screened: 2 boys<br>Number of participants included: 2<br>Number of participants followed up: 2<br>Number of withdrawals: none<br>Diagnosis of ADHD: DSM-III-R (subtype not stated)<br>Age: Dan 9 years, Bill 13 years<br>IQ: not stated<br>Methylphenidate naive: 100%<br>Ethnicity: not stated<br>Country: USA<br>Setting: not stated<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Not stated<br>**Exclusion criteria**<br>1. Not stated |
| Interventions | Participants were randomly assigned to different orders of 3 doses of methylphenidate and placebo<br>Mean methylphenidate dosage: not relevant<br>Administration schedule: once daily at breakfast<br>Duration of each medication condition: Dan received placebo for 3 days, and 5 days of treatment with 5 mg, 10 mg or 15 mg methylphenidate consecutively. Bill received placebo for 3 days, and 3 days of treatment with 5 mg, 10 mg or 15 mg methylphenidate consecutively<br>Washout before study initiation: treatment-naive<br>Medication-free period between interventions: 24 hours between doses<br>Titration period: none<br>Treatment compliance: Parents were instructed to initial a monitoring form each time they gave a dose to their child after breakfast. No further description of this was provided<br>Regarding the follow-up trial: Dan 15 mg; Bill 10 mg (5 mg twice daily) |
| Outcomes | **General behaviour**<br>1. Child Attention Problems Scale (CAP, 12-items; Barkley 1990): teacher-rated, at the end of each medication trial<br>**Non-serious adverse events**<br>1. Stimulants Drug Side Effect Rating Scale: rated by participants, parents and Bill's teacher at the end of each medication trial<br>No relevant outcomes measured in the follow-up phase |

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| Notes | Sample calculation: not relevant<br>Ethics approval: not stated<br>**Comments from study authors**<br>1. Although results from both studies are promising, they must be interpreted with great caution because various methodological and design features introduced threats to internal validity. For example, inclusion of a no-medication day between trial phases would be more in keeping with standard practice of clinical research trials of medication<br>2. Even though methylphenidate has a relative low half-life (4 to 6 hours), it is thought to be completely eliminated from the body within 24 hours of ingestion; a carry-over of effect from one trial to another may have occurred<br>**Key conclusion of study authors**<br>1. Curriculum-based measurement data collected during short medication trials can be used to select a dose of methylphenidate that is likely to be beneficial for a student's ongoing academic growth<br>**Comments from review authors**<br>1. As we do not know whether any of the children were intellectually disabled, we can use the study results only in sensitivity analyses<br>2. The article reports some side effects, but we could not obtain more information on this from the study authors; therefore, these data are not used in the review<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: no<br>Email correspondence with study author: January 2014. Wrote to study author to request additional information regarding ethics approval, intellectual disability, etc., but have not received a response |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The order of medication levels was determined randomly. In packing the envelopes, 1 of the study authors arranged the coded envelopes according to the randomly determined order of trials |
| Allocation concealment (selection bias) | Low risk | Each medication level was prepared and packed in separate envelopes by a pharmacist |
| Blinding of participants and personnel (performance bias) | Low risk | Each dose of methylphenidate and placebo was grounded into a powder, mixed with an inert compound, and was sealed in a small coloured drug capsule, so that doses were identical in appearance and taste. Thus, the pharmacist, the data collectors, the participants and their families did not know the order of drug administration |
| Blinding of outcome assessment (detection bias) | Low risk | Each dose of methylphenidate and placebo was grounded into a powder, mixed with an inert compound, and was sealed in a small coloured drug capsule, so that doses were identical in appearance and taste. Thus, the pharmacist, the data collectors, the participants and their families did not know the order of drug administration |
| Incomplete outcome data (attrition bias) | Low risk | All data were provided<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Unclear risk | No protocol was identified, and no answer was received from the study author |
| Vested interest bias | Low risk | National Association of School Psychologists<br>Conflicts of interest: not declared |

*Sumner 2010*

| Methods | Three-week, triple-blind, randomised, cross-over trial with 2 interventions<br>1. Methylphenidate or atomoxetine<br>2. placebo |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 31<br>Number of participants followed up: not stated<br>Number of withdrawals: 1<br>Diagnosis of ADHD: DSM-IV (subtype not stated)<br>Age: mean not stated (range 6 to 14 years)<br>IQ: not stated<br>Sex: not stated<br>Methylphenidate naive: not stated<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: none<br>Comedication: none<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. 6 to 14 years<br>2. ADHD, any subtype, according to DSM-IV criteria<br>3. ADHD symptoms of sufficient severity to warrant pharmacotherapy, but patient had never received the active medications evaluated in this study or had not exhibited significant treatment-limiting adverse effects while using them<br>**Exclusion criteria**<br>1. Enrolment in self contained special education classes<br>2. Females with prior onset of menses: positive urine pregnancy tests at enrolment<br>3. Structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmias or other serious cardiac abnormalities<br>4. Considered by the investigator to be medically inappropriate for inclusion in a study using placebo<br>5. Prior or present use of alcohol or illicit drugs<br>6. Major medical or neurological disorders that could affect motor activity, attention, school attendance or ability to follow the study protocol<br>7. Diagnosis of a current anxiety disorder, tics, Tourette's syndrome, major depressive disorder<br>8. History of bipolar disorder, dysthymia or psychosis, or a family history of Tourette's syndrome<br>9. Treatment with a monoamine oxidase inhibitor within 14 days before screening |
| Interventions | Participants were randomly assigned to 1 of 2 possible drug condition orders: placebo, low, medium doses of OROS methylphenidate; or low, medium doses of OROS methylphenidate, placebo<br>Doses: low (18 mg), medium (participants < 50 kg: 27 mg; participants > 50 kg: 36 mg)<br>Administration schedule: not stated<br>Duration of each medication condition: 1 week<br>Washout before study initiation: 1 week<br>Titration period: no<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. ADHD Rating Scale: clinician-rated, weekly<br>2. Conners' Parent Rating Scale - Revised: short form, parent-rated, weekly |

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| Notes | Sample calculation: no<br>Ethics approval: yes<br>**Comments from study authors (limitations)**<br>1. Small participant sample size<br>2. Short medication washout<br>3. Lack of information about prior ADHD medication use<br>4. Absence of a true placebo arm in a parallel design<br>**Key conclusions of study authors**<br>1. Use of an objective measure, coupled with more stringent treatment response thresholds, may better inform treatment decisions by clinicians and may reduce costs and enhance assay sensitivity in ADHD clinical trials<br>2. Longer-term, multi-centre, prospective, parallel-group studies incorporating true placebo arms and more heterogeneous participant populations are warranted to confirm these preliminary findings<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; exclusion of participants who have exhibited significant treatment-limiting adverse effects while treated with methylphenidate<br>Any withdrawals due to adverse events: not stated<br>Email correspondence with study authors: August to September 2013. We attempted to obtain supplemental information regarding characteristics of participants, withdrawals, funding and efficacy data from study authors but without success |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomly assigned to 1 of 2 treatment sequence groups |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Low risk | Triple-blinded: Study participants, their parents/guardians and clinicians were blinded to study assignment in terms of medications and dosing sequences. An unblinded prescribing physician and an unblinded study co-ordinator did not participate in clinical ratings. Placebo was matched to blinded medication, so that the 2 were indistinguishable |
| Blinding of outcome assessment (detection bias) | Low risk | See above |
| Incomplete outcome data (attrition bias) | Unclear risk | One participant withdrew before the placebo visit and was not included in these analyses |
| Selective reporting (reporting bias) | Unclear risk | No protocol was available |
| Vested interest bias | Unclear risk | It was not clear who sponsored the study, but someone did (see authors' affiliations)<br>Conflicts of interest: Calvin R. Sumner is an employee of and an equity holder for the study sponsor. Virginia S. Haynes, PhD, is an employee of 3i Global (Basking Ridge, NJ) and a paid consultant for the study sponsor. Martin H. Teicher, MD, PhD, served as paid consultant and clinical investigator for the sponsor. Jeffrey H. Newcorn, MD, serves as advisor and consultant for Lilly, Ortho-McNeil Janssen, Schering-Plough and Shire. He receives research support from Lilly, Ortho-McNeil Janssen and Shire |

*Sunohara 1999*

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| **Methods** | Cross-over trial with 3 arms<br>1. Methylphenidate: low dose<br>2. Methylphenidate: high dose<br>3. Placebo<br>Phases: 3 |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 20 (16 boys, 4 girls)<br>Number of participants followed up: 20<br>Number of withdrawals: not stated<br>Diagnosis of ADHD: DSM-III-R (subtype not stated)<br>Age: mean 10.5 years (range 10 to 12)<br>IQ: < 80<br>Methylphenidate naive: none<br>Ethnicity: not stated<br>Country: Canada<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder (n = 4), learning disability (n = 8)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Children 10 to 12 years of age meeting DSM-II-R criteria for ADHD recruited from Child Development Centre at Hospital for Sick Children, Canada<br>**Exclusion criteria**<br>1. Conduct disorder, externalising disorder, anxiety<br>2. IQ < 80 |
| **Interventions** | Participants were randomly assigned to low- (mean 0.28 mg/kg) and high-dose (mean 0.56 mg/kg) methylphenidate and placebo in the morning and afternoon<br>Duration of each medication condition: 2 days<br>Washout before study initiation: no<br>Titration period: no<br>Treatment compliance: not stated |
| **Outcomes** | **Non-serious adverse events**<br>1. Reported as adverse effects. There were 0 adverse effects at the higher dose for all children |
| **Notes** | Sample calculation: *n*ot stated<br>Ethics approval: *n*o information<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: unclear<br>**Key conclusion of study authors**<br>1. No adverse effects of the higher dose were reported for any children<br>Email correspondence with study authors: April 2014. Wrote to study authors to ask for additional data but have not received a reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not stated |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Unclear risk | Not stated |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not stated |
| Incomplete outcome data (attrition bias) | Unclear risk | Not stated |
| Selective reporting (reporting bias) | High risk | Not clear |
| Vested interest bias | High risk | Research was supported by a RESTRACOM graduate studentship for The Hospital for Sick Children Research Institute and Novartis Pharmaceuticals |

*Swanson 1998*

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| Methods | Randomized, double-blind, cross-over study with 6 interventions<br>1. Methylphenidate<br>2. Placebo<br>Adderall in 4 different doses<br>1. 5 mg<br>2. 10 mg<br>3. 15 mg<br>4. 20 mg |

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| Participants | Number of participants screened: 36.<br>Number of participants included: 33<br>Number of participants followed up: 29<br>Number of withdrawals: 4<br>Diagnosis of ADHD: DSM-IV (subtype not stated)<br>Age: mean 10.58 years (range 7 to 14)<br>IQ: > 80<br>Sex: 26 boys, 7 girls<br>Methylphenidate naive: 0%<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic (laboratory classroom)<br>Comorbidity: none<br>Comedication: none<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Age between 7 and 14 years<br>2. Diagnosis of ADHD by DSM-IV<br>3. History of clinically significant response to typical doses of methylphenidate (5 mg to 20 mg, b.i.d. or t.i.d.)<br>**Exclusion criteria**<br>1. Blood pressure outside 95th percentiles for age and sex<br>2. Wechsler Intelligence Scale for Children - Second Edition: score < 80<br>3. Abnormalities noted upon physical examination<br>4. Current treatment with a non-stimulant medication for ADHD<br>5. Comorbid disorder<br>6. History of aggressive behaviour serious enough to preclude participation in regular classroom activities |
| Interventions | Participants were randomly assigned to 1 of 36 possible drug condition orders of unknown dose of methylphenidate, placebo and 4 doses of Adderall<br>Mean methylphenidate dosage: not stated<br>Administration schedule: once, morning<br>Duration of each medication condition: 7 days<br>Washout before study initiation: not stated<br>Medication-free period between interventions: none<br>Titration period: none<br>Treatment compliance: 30 of 33 participants completed the 7-week trial |

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| Outcomes | **ADHD symptoms**<br>1. SKAMP Teacher Rating Scale, as modified by Greenhill into 2 domains of Attention and Deportment (i.e. positive behaviour): completed by 1 of the teachers after each 45-minute class period (i.e. every 1.5 hours on the Saturday of each week, the teacher monitoring behaviour rated each student on each item)<br>**Serious adverse events**<br>1. No unusual or serious side effects were noted in this study<br>**Non-serious adverse events**<br>1. After each classroom period (6 times per day), teachers assessed each student on the MTA 10-Item Stimulant Side Effects (SSE) rating scale<br>2. Parents completed a side effects rating scale that included SSE items plus an additional item (trouble sleeping) 3 times per day, on Monday, Wednesday and Friday of each week |
| Notes | Sample calculation: no<br>Ethics approval: not stated<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; only known methylphenidate responders were included<br>**Comments from study authors**<br>1. Laboratory classroom experience may represent a novel experience for participants, and this could alter response to medication<br>2. Group interactions in a classroom with 16 or 17 students with ADHD may be different from those in the typical classroom of 20 to 30 students including 1 to 2 children with ADHD<br>3. Behaviour of 16 to 17 students with ADHD in a classroom with a student:teacher ratio of about 8:1 may be different from that in a classroom with the typical ratio of 20:1 to 30:1<br>**Key conclusions of study authors**<br>1. This documentation of efficacy in a controlled study supports the addition of Adderall to the armamentarium of psychotropic medications for treatment of ADHD<br>2. Differences in time-response patterns of Adderall and methylphenidate may help tailor treatment to meet specific clinical needs of different children with ADHD<br>Email correspondence with study authors: January 2014. No reply has been received |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Latin-square design (with provisions for 36 participants) was used to determine the within-participant order of administration of the 6 medication conditions, so that for each of the first 6 weeks, approximately one sixth of participants would be assigned to each of the 6 conditions. Separate randomisation was used to determine assignment of conditions across participants for week 7, to provide an opportunity to make up missed weeks |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | For each condition, a pharmacist prepared a set of 7 identical capsules, all containing placebo (lactose), 1 of the 4 doses of Adderall or methylphenidate |
| Blinding of outcome assessment (detection bias) | Unclear risk | No information |
| Incomplete outcome data (attrition bias) | Unclear risk | 30 of 33 participants completed the 7-week trial; 98% of data were collected as planned. For each individual, missing data (1.1% for SKAMP, 0% for Stimulant Side Effects) were replaced by the average of values from adjacent time points (or adjacent values for session 1 or 6) |
| Selective reporting (reporting bias) | Low risk | No information |
| Vested interest bias | High risk | Supported by a grant from Richwood Pharmaceutical Company |

*Swanson 1999*

| Methods | Four-period, double-blind, randomised, cross-over trial with 2 interventions<br>1. Methylphenidate<br>2. Placebo<br>**Phases**<br>1. b.i.d.: 2 doses of immediate-release methylphenidate 4,5 hours apart<br>2. Flat: morning dose of 80% of b.i.d. morning dose and the rest at 30-minute intervals over 6 hours, starting 1.5 hours after first dose<br>3. Ascending: morning dose of 40% of b.i.d. morning dose and that rest as increasing doses at 30-minute intervals over 5 hours, starting 1.5 hours after first dose |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 38 (33 boys, 5 girls)<br>Number of participants randomly assigned: 34. Participants were randomly assigned to 1 of 4 possible drug condition orders<br>Number of participants followed up: 31<br>Number of withdrawals: 3<br>Diagnosis of ADHD: DSM-IV (subtype not stated)<br>Age: mean 9.2 years (range 7 to 12)<br>IQ: not stated<br>Methylphenidate naive: 0%<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic (laboratory classroom)<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Diagnosis of ADHD<br>2. Onset by 7 years of age<br>3. Receiving current treatment with methylphenidate doses of 5 to 15 mg administered 2 or 3 times per day<br>4. 7 to 12 years of age<br>**Exclusion criteria**<br>1. Not stated |
| Interventions | Participants were randomly assigned to 1 of 3 possible drug condition orders of methylphenidate and placebo<br>Mean MPH dosage: not stated. Nominal dose: 20 mg/d<br>Administration schedule: 30-minute intervals from 7:30 AM to 3:00 PM<br>Duration of each medication condition: 1 day<br>Washout before study initiation: none<br>Titration period: none (participants were kept on current standard treatment in-between trial days)<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. Swanson, Kotkin, Agler, M-Flynn and Pelham Scale (SKAMP): teacher-rated, 4 times during the day<br>2. Conners, Loney and Milich Scale (CLAM): teacher-rated, 4 times during the day |

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| **Notes** | Sample calculation: no<br>Ethics approval: yes<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Comment from study authors**<br>1. Of the 38 children recruited for this trial, only 34 entered<br>**Key conclusion of study authors**<br>1. Acute tolerance to methylphenidate appears to exist<br>**Comment from review authors**<br>1. Publication includes 2 studies: In study I, relative efficacy was determined for 3 dosing patterns of methylphenidate vs placebo. In study II, tolerance was assessed by comparison of 3-times-a-day regimens of methylphenidate only. The latter is not part of the data extraction<br>Email correspondence with study authors: May 2014. Emailed study authors to ask for additional information. No reply has been received |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | On subsequent Saturdays, each child received (in random order) 1 of 3 possible drug condition orders of methylphenidate and placebo |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | All treatments were administered in identical capsules |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not stated |
| Incomplete outcome data (attrition bias) | High risk | Only completers were followed up |
| Selective reporting (reporting bias) | Low risk | No protocol was published. All pre-specified outcomes of interest have been reported |
| Vested interest bias | High risk | Supported by ALZA Corporation, Palo Alto, California |

### *Swanson 2002a*

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| **Methods** | Randomised, double-blind, cross-over design<br>1. Immediate-release methylphenidate t.i.d. or methylphenidate experimental administration<br>2. Placebo |

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|---|---|
| Participants | Number of participants screened: not stated<br>Number of participants included: 32 (28 boys, 4 girls)<br>Number of participants followed up: 30<br>Number of withdrawals: 2<br>Diagnosis of ADHD: DSM-IV (combined (93.8%), hyperactive-impulsive (6.2%), inattentive (0%))<br>Age: mean 9.9 years (range 7 to 13)<br>IQ: not stated<br>Methylphenidate naive: 0%<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic (laboratory classroom)<br>Comorbidity: 0%<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. ADHD<br>2. Normal blood pressure<br>3. Not physically ill<br>4. Able to understand that they could withdraw from the study at any time<br>**Exclusion criteria**<br>1. Oppositional defiant disorder<br>2. Conduct disorder<br>3. Mood disorders<br>4. Anxiety disorders |
| Interventions | Participants were randomly assigned to 1 of 3 possible drug condition orders of 5 mg, 10 mg or 15 mg t.i.d., or 18 mg/d, 36 mg/d or 54 mg/d administered in bolus at 7:30 AM and once every 30 minutes for 8 hours of methylphenidate and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: 3 time points<br>Duration of each medication condition: 1 day<br>Washout before study initiation: not stated<br>Medication-free period between interventions: none<br>Titration period: none<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. Swanson, Kotkin, Agler, M-Flynn and Pelham Scale (SKAMP)<br>**General behaviour**<br>1. Actigraph activity measurements<br>**Non-serious adverse events**<br>1. Proof of Concept Study (n = 32)<br>2. Teachers: appetite loss (t.i.d., n = 6; ascending, n = 7)<br>3. Parent reports of somatic complaints (primarily headache or stomachache): t.i.d. methylphenidate (n = 9), ascending (n = 5)<br>4. Sleep onset was delayed slightly in the medication conditions (ascending, 0.65 h; t.i.d., 0.55 h) |

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| **Notes** | Sample calculation: not stated<br>Ethics approval: yes<br>**Comments from study authors (limitations)**<br>1. Lack of normal control participants<br>2. Use of subjective rating measures<br>3. Use of different actigraph modes of operation<br>4. Lack of a systematic evaluation of whether baseline levels of behaviour were predictive of medication effects<br>**Key conclusions of study authors**<br>1. Combination of an initial bolus of methylphenidate and an ascending pattern of small doses significantly decreased hyperactivity and reduced inappropriate behaviour<br>2. Studies showed acute tolerance to clinical doses of methylphenidate and application of this: creation of an ascending drug delivery pattern (OROS) of rapid onset and with long duration of effect<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: All children in the trial were undergoing treatment with methylphenidate when they were enrolled<br>Email correspondence with study authors: Study authors were contacted twice by email and were asked for much supplemental information regarding data, but we have received no data; therefore, most of the data from this study cannot be used in this review |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "Randomized, 3-way, crossover trial in which a double-blind, double-dummy procedure was used" |
| Allocation concealment (selection bias) | Unclear risk | Not enough information |
| Blinding of participants and personnel (performance bias) | Unclear risk | Not enough information |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not enough information |
| Incomplete outcome data (attrition bias) | Unclear risk | Not enough information<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no, but all children in the trial were undergoing treatment with methylphenidate when they were enrolled |
| Selective reporting (reporting bias) | Low risk | "Two additional items developed (from SKAMP) for the NIMH Collaborative Multisite Multimodal Treatment Study of Children With ADHD (MTA) (Greenhill et al., 2001) were included in the classroom ratings but were not included in the analyses of this study" |
| Vested interest bias | High risk | "Supported by the ALZA Corporation" |

*Swanson 2002b*

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| **Methods** | Randomized, 3-way, cross-over trial with 2 interventions<br>1. Methylphenidate (t.i.d. or OROS extended release)<br>2. Placebo<br>Phases: 3 |

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|---|---|
| Participants | Number of participants screened: not stated<br>Number of participants included: 64<br>Number of participants followed up: 59<br>Number of withdrawals: 3<br>Diagnosis of ADHD: DSM-IV (combined (82.8%), hyperactive-impulsive (not stated), inattentive (not stated))<br>Age: mean 9.2 years (range 6 to 12)<br>IQ: not stated<br>Sex: 81.3% boys<br>Methylphenidate naive: none<br>Ethnicity: Caucasian (82.8%), African American (not stated), Asian (not stated), Hispanic (not stated)<br>Country: USA<br>Setting: out-patient clinic (laboratory classroom)<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. DSM-IV criteria for ADHD diagnosis, treated with immediate-release methylphenidate 5 mg to 15 mg b.i.d. or t.i.d.<br>**Exclusion criteria**<br>1. Not stated |
| Interventions | Participants were randomly assigned to 1 of 6 possible drug condition orders of 5 mg, 10 mg or 15 mg t.i.d., or 18 mg, 36 mg or 54 mg OROS methylphenidate and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: t.i.d. 7:30 AM, 11:30 AM and 3:30 PM; OROS 7:30 AM<br>Duration of each medication condition: 1 week<br>Washout before study initiation: not stated<br>Medication-free period between interventions: not stated<br>Titration period: none<br>Treatment compliance: no measure |
| Outcomes | **ADHD symptoms**<br>1. Swanson, Kotkin, Agler, M-Flynn and Pelham Scale (SKAMP): rated by laboratory school teacher on attendance on Saturdays<br>2. Conners, Loney and Milich Scale (CLAM): rated by parent and community teacher on Fridays<br>3. Swanson, Nolan and Pelham (SNAP): rated by community teacher and parent at the end of each week<br>**Non-serious adverse events**<br>1. "In addition to the effectiveness and efficacy measures, adverse effects were actively solicited and assessed and information about sleep, appetite, and tics was collected using a parent questionnaire"<br>2. Vital signs (blood pressure, pulse) after each classroom session on Saturdays in the laboratory school setting<br>3. Sleep: activity monitoring and parental assessment |

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| **Notes** | Sample calculation: not stated<br>Ethics approval: not stated<br>**Key conclusion of study authors**<br>1. Pharmacokinetic/Pharmacodynamic modelling provided the target for a novel drug delivery pattern to overcome these shortcomings: an initial bolus to elicit a rapid response and an ascending pattern of drug delivery to maintain constant effects<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; "The children with ADHD in the proof-of-concept and proof-of-product studies were selected based on a history of clinical response to stimulant medication, and this limits the extrapolation of the findings to the drug-naive population"<br>Any withdrawals due to adverse events: no<br>Email correspondence with study authors: March 2014. We contacted study authors twice by email and asked for supplemental information regarding data, but we have received no data; therefore most of the data from this study cannot be used in this review |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not stated |
| Allocation concealment (selection bias) | Unclear risk | Double-blind procedures were implemented by administration of methylphenidate or placebo in capsules |
| Blinding of participants and personnel (performance bias) | Unclear risk | Double-blind, double-dummy procedure was used to disguise the 3 treatments |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not stated |
| Incomplete outcome data (attrition bias) | High risk | Children with ADHD in proof-of-concept and proof-of-product studies were selected on the basis of a history of clinical response to stimulant medication; this limits extrapolation of findings to the drug-naive population |
| Selective reporting (reporting bias) | Unclear risk | No protocol |
| Vested interest bias | High risk | Supported by ALZA Corporation |

*Swanson 2004b*

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| **Methods** | Multi-centre, double-blind, double-dummy, placebo-controlled, cross-over study in an analogue classroom setting comparing 3 treatment conditions<br>1. Metadate CD<br>2. Concerta<br>3. Placebo<br>Each treatment intervention lasted a week |

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| Participants | Number of participants screened: 214<br>Number of participants included: 184<br>Number of participants followed up: 157/184 ITT<br>Number of withdrawals: 27<br>Diagnosis of ADHD: DSM-IV (combined (82.2%), hyperactive-impulsive (4.8%), inattentive (13.0 %))<br>Age: mean 9.6 years (range 6 to 12)<br>IQ: > 80<br>Sex: 131 boys, 48 girls<br>Methylphenidate naive: none<br>Ethnicity: Caucasian (70%), African American (11.5%), Asian (1.7%), Hispanic (12.5%), other (5.3%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: Approximately 25% had a comorbid condition; anxiety and oppositional defiant disorder were most frequent. Females had a greater rate of comorbid anxiety disorder (from Sonuga-Barke 2007). Anxiety: 20.8 girls, 5.9 boys. Oppositional defiant disorder: 12.5 girls, 8.8 boys. Insomnia: 2.1 girls, 5.1 boys.<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Children (6 to 12 years old) who had clinical diagnoses of a DSM-IV subtype of ADHD (inattentive type, hyperactive-impulsive type or combined type) were recruited<br>2. Treatment with methylphenidate in doses of 10 mg/d to 60 mg/d (5 mg to 20 mg per administration, 1 to 3 times a day)<br>3. Children were deemed otherwise healthy by means of a medical history, physical examination, vital signs measurement (blood pressure, heart rate, respiration and temperature) and clinical laboratory assessments (haematology and urinalysis)<br>4. In addition, children had to demonstrate the ability to swallow placebo study treatment capsules whole and without difficulty<br>5. Receiving an approved form of methylphenidate with demonstrated clinical improvement during this treatment<br>**Exclusion criteria**<br>1. Intelligence quotient < 80 or inability to follow or understand study instructions<br>2. Pregnancy<br>3. History of seizure or tic disorder<br>4. Family history of seizure or Gilles de La Tourette's syndrome<br>5. Congenital cardiac abnormality<br>6. History of cardiac disease including myocardial infarction within 3 months of study entry<br>7. Glaucoma<br>8. Hyperthyroidism<br>9. History of substance abuse or caretaker with history of substance abuse<br>10. Concurrent chronic or acute illness or other condition that might confound study rating measures<br>11. Documented allergy or intolerance to methylphenidate<br>12. Use of an investigational drug within 30 days of study entry<br>13. Use of concomitant medication that could interfere with assessment of efficacy and safety of study treatments |

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| Interventions | Participants were randomly assigned to 1 of 6 possible drug condition orders of Metadate CD, Concerta and placebo<br><br>Dose: Children treated with low doses (20 mg/d) of methylphenidate were randomly assigned to receive Metadate CD 20, Concerta 18 or placebo; those treated with medium doses (20 to 40 mg/d) were randomly assigned to receive Metadate CD 40, Concerta 36 or placebo; children treated with high doses (40 mg/d) were randomly assigned to receive Metadate CD 60, Concerta 54 or placebo<br><br>Administration schedule: once daily in the morning<br><br>Duration of each medication condition: 7 days<br><br>Washout before study initiation: no<br><br>Medication-free period between interventions: not stated<br><br>Titration period: none<br><br>Treatment compliance: Regarding the medicine, not stated. 157 received all 3 levels of treatment and participated in all 7 classroom sessions |
| Outcomes | **ADHD symptoms**<br><br>1. Swanson, Kotkin, Agler, M-Flynn and Pelham Scale (SKAMP): tested on day 7 in the laboratory school by 2 trained observers. Time points for the test (after ingestion of medication/placebo): h = 0, h = 1.5, h = 3.0, h = 4.5, h = 6, h = 7, h = 12.0<br>2. Swanson, Nolan and Pelham (SNAP): parent-rated, administered twice during each treatment week on days 3 and 6<br><br>**Non-serious adverse events**<br><br>1. Adverse events reported by participant or parent (guardian). Reported adverse events were characterised (by the investigator at each site) as mild, moderate or severe<br>2. Barkley Side Effects Rating Scale: rated symptoms during past week and completed weekly by parent (guardian) on day 6<br>3. Heart rate: measured before doses were taken and at the following time points after ingestion: h = 1.5, h = 3.0, h = 4.5, h = 6, h = 7, h = 12.0<br>4. Blood pressure: measured before doses were taken and at the following time points after ingestion: h = 1.5, h = 3.0, h = 4.5, h = 6, h = 7, h = 12.0 |
| Notes | Sample calculation: yes<br><br>Ethics approval: yes<br><br>**Comments from study authors**<br><br>1. In ANOVA of measures of blood pressure and heart rate, only 2 statistically significant differences related to treatment emerged: systolic blood pressure at hour 7.5, and pulse rate at hour 1.5<br>2. Site differences in this study deserve some comment because this is a common finding in multi-site studies. Site difference was most prominent for subjective outcome measures on the SKAMP Rating Scale, which depends on the training of observers (difficult to equate across sites) and the context of the classroom (controlled but still may vary across sites because of class size, physical space and other factors that may not be standardised)<br>3. Regarding analysis of sex (Sonuga-Barke 2007): Despite the relatively large number of females in the sample, power was insufficient to include dose level as a factor in the analysis<br>4. Given the manner in which sex effects appeared to vary across the day, present results may be consistent with pharmacokinetic or pharmacodynamic explanations, or a combination of the 2. Early and late sex-related differences in clinical effect may be independent of one another or linked. Several possible explanations seem worth testing. The superior methylphenidate response shown by females in the early part of the day may result from greater sensitivity to methylphenidate or from higher methylphenidate plasma concentrations due to increased rates or efficiency of absorption of immediate-release components. The steeper decline in methylphenidate response shown by females may be a consequence of earlier but normative clearance of methylphenidate following more rapid absorption, or may be indicative of more rapid clearance in females than in males<br><br>Limitations |

1. Laboratory setting lacks many features of the natural environment of the home and school. Thus, it is not certain whether the patterns reported here would be observed in school settings in which an ADHD student would be in a classroom in which most students not affected by this disorder
2. Study was designed to contrast total absorbed daily doses that were approximately equal, although this resulted in differences in initial bolus doses of the 2 active treatments (Metadate CD and Concerta). In this study, doses were not evaluated that were equal to the initial bolus doses of immediate-release methylphenidate, which would provide another test of the PK/PD model
3. Effects of both Metadate CD and Concerta in the low-dose subgroup were smaller than in the high-dose subgroup, but we do not know whether a higher dose in the low-dose subgroup would have increased the ES. Lack of tailoring to achieve rigorous experimental control may be another limitation of this study
4. This study included only patients who already were being treated successfully with methylphenidate. This means that severe and marked adverse events are unlikely to be seen in this study, and it is possible that lack of effect on side effects rating scale factors other than sleep/appetite may occur more readily in medication-naive patients. Furthermore, it is important to recognise that this was a secondary analysis of a study powered to show non-equivalence between the 2 methylphenidate formulations in terms of efficacy, not in terms of adverse events
5. Sonuga-Barke 2009: This study included only patients who already were being treated successfully with methylphenidate. This means that severe and marked adverse events are unlikely to be seen in this study
6. Trial was also underpowered for detecting rare events that could be severe. Measures of adverse events were derived only from parent ratings, not from direct observations of behaviour
7. Significant side effects not measured by the Barkley Side Effects Rating Scale may have occurred

**Key conclusions of study authors**

1. Once-daily doses of Metadate CD and Concerta produced statistically significantly different PD effects on surrogate measures of behaviour and performance among children with attention deficit hyperactivity disorder in the laboratory school setting
2. As predicted by the PK/PD model, superiority at any point in time was achieved by the formulation with the highest expected plasma methylphenidate concentration

**Regarding sex differences**

1. Dose titration of once-daily formulations of methylphenidate ideally should be based on systematic evidence of response at different periods across the day
2. Responses of female patients may require additional assessments later in the day to determine optimal dose

**Comment from review authors**

1. Compared ratings on sex from SKAMP. However only compared the 2 medication conditions vs each other, not medication conditions vs placebo; therefore we cannot use these analyses

Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: *y*es

Any withdrawals due to adverse events: Three study participants discontinued because of adverse events that were judged to be unrelated to medications (gastroenteritis: Concerta (n = 1); fever: placebo (n = 1); sunburn: placebo (n = 1))

Email correspondence with study authors: June 2014. We emailed study authors to obtain supplemental data. Unfortunately, data in the correct format are no longer accessible

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomised |
| Allocation concealment (selection bias) | Unclear risk | Randomised |
| Blinding of participants and personnel (performance bias) | Low risk | Double-blind, double-dummy. Treatments were packaged according to a double-dummy design. Each treatment pack contained a 1-week supply of study treatment, with each day's supply consisting of 1 large capsule to accommodate the size of any dose level of Concerta (containing Concerta or placebo) and, depending on dose level, between 1 and 3 smaller Metadate CD-sized capsules (containing Metadate CD or placebo) |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not stated |
| Incomplete outcome data (attrition bias) | Low risk | Data from participants finishing the whole study (n = 157) and from the ITT population (n = 184)<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Unclear risk | No information |
| Vested interest bias | High risk | Study was funded by Celltech Pharmaceuticals Incorporated<br>Conflicts of interest: Some study authors are consultants for pharmaceutical companies |

### *Symons 2007*

| Methods | Prospective, randomised, double-blind, placebo-controlled, cross-over, single-case designs were used to evaluate methylphenidate administration for 3 school-aged children with cerebral palsy and comorbid ADHD symptoms<br>1. Low-dose methylphenidate<br>2. High-dose methylphenidate<br>3. Placebo<br>Phases: 4 (including baseline) |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 2 (1 boy, 1 girl)<br>Number of participants followed up: 2<br>Number of withdrawals: none<br>Diagnosis of ADHD: DSM-IV (combined (100%), hyperactive-impulsive (0%), inattentive (0%))<br>Age: mean 10.4 years (range 9 to 11)<br>IQ: > 70. Participant 2 = 92 non-verbal and 96 performance non-verbal (range not stated)<br>Methylphenidate naive: not stated<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: cerebral palsy (100%), mild cognitive impairment (100%), autism spectrum disorder (50%), physical impairment (50%), learning disability (50%), other health impairment (50%)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. DSM-IV diagnosis of ADHD<br>2. Cerebral palsy<br>3. Attending public elementary schools |
| Interventions | Participants were randomly assigned to 1 of 3 possible drug condition orders of methylphenidate (low or high dose) and placebo<br>Mean methylphenidate dosage: 2 doses of methylphenidate administered: low (0.3 mg/kg) and high (0.5 mg/kg)<br>Administration schedule: once daily, mornings, before the child's school arrival<br>Duration of each medication condition: Order of drug/placebo administration was randomly assigned, and administration was provided for 5 consecutive school days in each condition. Drug treatment was not administered on weekends<br>For participant 2, the order of administration was as follows: baseline, low dose, placebo, high dose<br>For participant 3, the order of administration was as follows: baseline, placebo, low dose, high dose<br>Washout before study initiation: not stated<br>Medication-free period between interventions: weekends<br>Titration period: not stated<br>Treatment compliance: not stated |
| Outcomes | **General behaviour**<br>1. Direct observation protocol based on a 10-second partial interval (1/0) for stereotyped and disruptive behaviours and time sampling for task-related behaviour was used to code data collected directly from each child's classroom for two 30-minute sessions on 2 separate days for each week of the trial. Student and teaching staff behaviours were recorded using handheld digital cameras. An observer designated as the primary observer coded all videotaped sessions for that target student. A secondary observer independently coded 20% of randomly selected videotaped sessions for each student<br>**Non-serious adverse events**<br>1. No parent or teacher reports described significant side effects associated with either dose level (e.g. changes in sleep, eating, etc.) |

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| **Notes** | Sample calculation: no<br>Ethics approval: not stated<br>**Key conclusions of study authors**<br>1. Low-dose but not high-dose methylphenidate administration resulted in clinically significant reductions in directly observed stereotyped and disruptive behaviours for 3 elementary school–aged children with cerebral palsy<br>2. For 2 of the children, stereotyped behaviour was exacerbated during high-dose administration<br>3. Finally, no change in attending, as measured by direct observation of task-related behaviour, was noted<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: May 2014. Emailed study author to request additional information but have not received a reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Order of drug/placebo administration was randomly assigned |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Low risk | Parents, school personnel (i.e. teachers, teacher assistants) and research assistants responsible for observational data collection and coding were kept blind to drug/placebo conditions |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not stated |
| Incomplete outcome data (attrition bias) | Unclear risk | Not stated<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Unclear risk | No protocol |
| Vested interest bias | Unclear risk | Not stated<br>Conflicts of interest: This work was supported, in part, by a McKnight Land-Grant Professorship to Frank Symons |

*Szobot 2004*

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| **Methods** | Four-day, double-blind, placebo-controlled, randomised, fixed dose-escalating of methylphenidate, parallel-group trial |

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| Participants | Number of participants screened: not stated<br>Number of participants included: 36 (all boys)<br>Number of participants randomly assigned: methylphenidate 19, placebo 17<br>Number of participants followed up: methylphenidate 19, placebo 17<br>Number of withdrawals: none<br>Diagnosis of ADHD: DSM-IV, combined (methylphenidate 84.6%, placebo 76.5%)<br>Age: mean 11.6 years<br>IQ: mean 94.7<br>Methylphenidate naive: no psychiatric medication for the past 6 months<br>Ethnicity: European-Brazilian (89%)<br>Country: Brazil<br>Setting: out-patient clinic<br>Comorbidity: Conduct disorder and oppositional defiant disorder (methylphenidate 58.8%, placebo 68.4%), depressive disorder (methylphenidate 5.2%, placebo 5.9%), multiple anxiety disorder (methylphenidate 5.2%, placebo 0%), tic disorder (methylphenidate 0%, placebo 5.9%)<br>Comedication: not stated<br>Sociodemographics: low- to middle-income families<br>**Inclusion criteria**<br>1. Diagnosis of ADHD according to DSM-IV criteria (American Psychiatric Association, 1994)<br>2. Between 8 and 17 years old<br>3. Male sex<br>**Exclusion criteria**<br>1. Presence of any neurological or significant clinical disease<br>2. Presence of bipolar disorder or any substance abuse/dependence disorder<br>3. Use of any psychiatric medication in the previous 6 months<br>4. Estimated IQ < 70 |
| Interventions | Participants were randomly assigned to methylphenidate or placebo<br>Mean methylphenidate dosage: 0.72 mg/kg/d<br>Administration schedule: twice a day: morning and lunchtime<br>Duration of intervention: 4 days<br>Titration period: first day 0.35 mg/kg<br>Treatment compliance: good |
| Outcomes | **ADHD symptoms**<br>1. Conners' Abbreviated Rating Scale (ABRS)<br>**Quality of life**<br>1. Children's Global Assessment Scale (CGAS). CGAS was scored by a child psychiatrist<br>**Non-serious adverse events**<br>1. A research assistant called each family to check side effects. No participants had to interrupt the protocol because of side effects |

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| **Notes** | Sample calculation: no<br>Ethics approval: approved by the Ethical Committee of the HCPA (approved as an IRB by the Office for Human Research Protections, USA)<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Comments from study authors**<br>1. Our results extend the efficacy of methylphenidate for ADHD core symptoms as extensively demonstrated in clinical trials with samples from developed countries to samples from developing countries, for whom a diverse culture may modulate clinical presentation of the disorder<br>2. This study's rate of robust response with methylphenidate might reflect the short duration (4 days) of the clinical trial<br>3. Results may not generalise to other different sociocultural groups or to patients from the community<br>4. Side effects were not objectively registered<br>**Key conclusion of study authors**<br>1. Methylphenidate group had a significantly greater decrease in ABRS scores and a significantly greater increase in CGAS scores when compared with the placebo group (P value < 0.01)<br>Email correspondence with study authors: October 2013. We received from the study authors supplemental information regarding blinding and allocation concealment |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Participants were randomly assigned on the basis of a computer-derived algorithm (EPIINFO6) |
| Allocation concealment (selection bias) | Low risk | Only the doctor performing the randomisation knew the allocation, and he had nothing to do with data collection |
| Blinding of participants and personnel (performance bias) | Low risk | Double-blind: Participants, parents and all research team members who had contact with participants. Both methylphenidate and placebo pills were manufactured by a single pharmaceutical company; they had the same format and colour and were given to participants in 4 different blisters |
| Blinding of outcome assessment (detection bias) | Low risk | All research team members who had contact with participants |
| Incomplete outcome data (attrition bias) | Low risk | None<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo-responders): no |
| Selective reporting (reporting bias) | Unclear risk | No information |
| Vested interest bias | High risk | This work was supported by research funds from Hospital de Clínicas de Porto Alegre, FAPERGS and NOVARTIS |

### *Szobot 2008*

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| **Methods** | Cross-over trial with 2 interventions<br>1. SODAS methylphenidate<br>2. Placebo<br>Phases: 2- or 3-week phases, with each group receiving placebo or SODAS methylphenidate |

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| Participants | Number of participants screened: 25 from a previous ADHD/substance misuse study and 15 through advertising<br>Number of participants included: 16<br>Number of participants followed up: 16<br>Number of withdrawals: 2 (both from group A; withdrawal rate 12.5%)<br>Diagnosis of ADHD: DSM-IV (combined 12 (75%), inattentive 3 (18.75%), hyperactive/impulsive (n = 1))<br>Mean age: group A 17.5 years (SD 2.33), group B 17.38 (SD 2.2)<br>IQ: group A 79.43 (SD 16.66), group B 84.75 (SD 21.16)<br>Sex: all boys (100%)<br>Methylphenidate naive: 100%<br>Ethnicity: European-Brazilian (group A 3 (37.5%), group B 7 (87.5%))<br>Country: Brazil<br>Setting: out-patient clinic<br>Comorbidity: conduct disorder (group A 100%, group B 75%); oppositional defiant disorder (group A 25%, group B 37.5%); depression (group A 12.5%, group B 25%)<br>Comedication: yes (marijuana and cocaine); group A: marijuana (100%) and cocaine (50%); group B: marijuana (87.5%) and cocaine (37.5%)<br>Sociodemographics: divorced parents (group A 37.5%, group B 50%); socioeconomic group A + B + C (group A 50%, group B 87.5%); group D + E (group A 50%, group B 12.5%)<br>**Inclusion criteria**<br>1. 15 to 21 years of age<br>2. Male<br>3. Current diagnosis of abuse of marijuana or cocaine (K-SADS-E and MINI)<br>4. Current diagnosis of ADHD: Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiological Version (K-SADS-E)<br>5. Stimulant naive<br>**Exclusion criteria**<br>1. Absence of responsible adult - to inform on childhood psychopathology and to take responsibility for medication and/or the need for in-patient care for substance misuse or psychiatric comorbidity<br>2. Primary psychiatric condition requiring immediate treatment (e.g. moderate/severe depression) |
| Interventions | Participants were randomly assigned to 1 of 2 possible drug condition orders of methylphenidate and placebo<br>Mean SODAS methylphenidate dosage: 0.3, 0.7 and 1.2 mg/kg/d for weeks 1, 2 and 3 for group A, and for weeks 4, 5 and 6 for group B<br>Administration schedule: morning dose time points<br>Duration of each medication condition: 3 weeks<br>Washout before study initiation: no<br>Medication-free period between interventions: 24 hours<br>Titration period: none<br>Treatment compliance: "Study compliance was assessed by self-report, mother's report and pill counting" |

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| Outcomes | **ADHD symptoms**<br>1. Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiological Version (K-SADS-E), for diagnosis<br>2. Swanson, Nolan and Pelham scale, Fourth Edition (SNAP-IV)<br>**General behaviour**<br>1. Clinical Global Impression (CGI) Scale<br>**Serious adverse events**<br>1. Barkley Side Effect Rating Scale (SERS)<br>**Non-serious adverse events**<br>1. Barkley Side Effect Rating Scale (SERS) |
| Notes | Sample calculation: not stated<br>Ethics approval: "The project was approved by the Institutional Review Board (IRB) of Hospital de Clinicas de Porto Alegre (approved as an IRB by the Office for Human Research Protections, United States of America, IRB 00000921"<br>**Comments from study authors**<br>1. In the present study, SODAS methylphenidate was significantly superior to placebo in reducing ADHD symptoms and improving global functioning for all main outcome measures (SNAP-IV and CGI scores)<br>2. No treatment effect on illicit substance use disorders was noted, and methylphenidate-SODAS was well tolerated, despite causing greater appetite reduction than was seen with placebo<br>**Key conclusions of study authors**<br>1. SODAS methylphenidate was more effective than placebo in reducing ADHD symptoms in a non-abstinent out-patient sample of adolescents with comorbid substance use disorders<br>2. Randomised clinical trials, with larger samples and substance use disorder interventions, are recommended<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: One withdrawal resulted from a participant feeling "worse", "more restless"<br>Email correspondence with study authors: May 2014. We received supplemental information from study authors |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | High risk | "One of the investigators (LAR) randomized the 16 subjects into groups A or B and prepared weekly blisters of medications for each participant" |
| Allocation concealment (selection bias) | High risk | Not stated |
| Blinding of participants and personnel (performance bias) | Low risk | "A pharmacist packaged mPH-SODAS and matching placebo in capsules so that the MPH-SODAS and placebo could not be visually differentiated" |
| Blinding of outcome assessment (detection bias) | Low risk | From author correspondence: All persons who evaluated outcome measures were blinded |
| Incomplete outcome data (attrition bias) | Unclear risk | No information<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): unclear |
| Selective reporting (reporting bias) | Unclear risk | No information |
| Vested interest bias | High risk | "The ADHD outpatient program receives research support from Bristol-Myers Squibb, Eli-Lilly, Janssen-Cilag and Novartis"<br>Conflicts of interest: Study authors are consultants and speakers for various companies |

*Tannock 1989*

| Methods | Within-participant, cross-over trial with 3 interventions<br>1. Methylphenidate 0.3 mg/kg<br>2. Methylphenidate 1 mg/kg<br>3. Placebo<br>Two different drug conditions each day |
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| Participants | Number of participants screened: 16<br>Number of participants included: 19<br>Number of participants followed up: 12 (10 boys, 2 girls)<br>Number of withdrawals: none<br>Diagnosis of ADHD: DSM-III ADD-H (equivalent to 'combined' in later classifications)<br>Age: mean 8.4 years (range 6 to 11)<br>IQ: mean 105<br>Methylphenidate naive: Five received methylphenidate previously. Three were taking methylphenidate at the time of referral and had a 48-hour pre-trial washout<br>Ethnicity: not stated<br>Country: Canada<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder (n = 4), learning difficulties (n = 8; according to school record and defined as < 25th percentile on 1 or more subtests within the Wide Range Achievement Test (WRAT-R))<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Thought by referring physician to have ADHD<br>2. Confirmed through assessment by 2 child psychiatrists using the Parent Interview Child Symptoms Questionnaire<br>3. Confirmed by teacher information on Conners' Teacher Questionnaire, Rutter B Questionnaire and the Swanson, Nolan and Pelham Questionnaire<br>**Exclusion criteria**<br>1. Full-scale WISC-R < 80<br>2. Exclusive diagnosis of emotional or conduct disorder; major neurological, physical or sensory impairment; and/or any contraindication for use of methylphenidate (e.g. tics, seizures, heart disease) |
| Interventions | Participants were randomly assigned to 1 of 3 possible drug condition orders of 0.3 mg/kg or 0.6 mg/kg methylphenidate and placebo<br>Mean methylphenidate dosage: not stated.<br>Administration schedule: Interval of 4 hours separated morning and afternoon doses<br>Duration of each medication condition: not stated<br>Washout before study initiation: 4 hours<br>Titration period: none<br>Treatment compliance: not stated |
| Outcomes | **Non-serious adverse events**<br>1. Treatment-emergent side effects (e.g. stomach distress, pallor, mood swings, tics)<br>2. Pulse and blood pressure readings taken in sitting position immediately before medication and again 1 hour after administration of dose |

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| **Notes** | Sample calculation: not stated<br>Ethics approval: not stated<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: not stated<br>**Key conclusions of study authors**<br>1. Behavioural and academic improvements produced by a dose of 0.3 mg/kg in the morning were no longer evident in the afternoon<br>2. 1 mg/kg methylphenidate produced behavioural improvements that were clinically and statistically discernible in the afternoon, although academic improvements had dissipated<br>3. Carryover effects of methylphenidate into the afternoon were discernible with 1.0 mg/kg but not with 0.3 mg/kg<br>**Comment from review authors**<br>1. Outcomes for ADHD symptoms were not appropriate for this study, so only adverse effects were examined<br>Email correspondence with study authors: sent email to study authors to ask for additional information but have not received a reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "The order of medication condition was randomized with the restrictions that each child receive two different medication conditions each day (e.g. high, low) occur with equal frequency in the morning and afternoon" "The order of these six combinations was randomized for each child" |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Low risk | "The methylphenidate and placebo were packaged in coloured gelatin capsules by the hospital pharmacist to avoid detection of dose and taste, packaged in individual envelopes and dispensed by project staff 1 hour before testing" |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not stated |
| Incomplete outcome data (attrition bias) | Unclear risk | Not stated<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | Not stated |
| Vested interest bias | Low risk | Jointly funded by Ontario Mental Health Foundation (Grant No. 963-86/88) and Health and Welfare Canada (Grant No. 6606-3166-42)<br>Conflict of interest: Study authors' affiliations were not declared |

### *Tannock 1992*

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| **Methods** | Cross-over trial with 2 interventions<br>1. Methylphenidate low dose<br>2. Methylphenidate high dose<br>3. Placebo<br>Phases: 3 separate drug conditions: placebo, low-dose (0.3 mg/kg) and high-dose (1.0 mg/kg) medication, with 2 test sessions each. Drug conditions changed on a daily basis: 6 test sessions plus baseline practice session |

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| Participants | Number of participants included: 26<br>Participants were randomly assigned to 1 of 2 possible drug condition orders<br>Number of participants followed up: 23<br>Number of withdrawals: 3<br>Diagnosis of ADHD: DSM-III (subtype not stated)<br>Age: mean 9.2 years (range not stated)<br>IQ: mean 105.9 (SD 10.5)<br>Sex: 24 boys, 2 girls<br>Methylphenidate naive (not clear; "9 children receiving stimulant medication prior to the present study")<br>Ethnicity: not stated<br>Country: Canada<br>Setting: hospital/out-patient department<br>Comorbidity: 12<br>Comedication: not clear<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Diagnosis of ADHD confirmed<br>2. Child had to be scheduled to receive a trial with methylphenidate independent of the present investigation<br>**Exclusion criteria**<br>1. Wechsler Intelligence Scale for Children - Revised: < 80<br>2. Exclusive DSM-III diagnosis of Conduct disorder or an Emotional disorder<br>3. Major neurological, physical or sensory impairment |
| Interventions | Participants were randomly assigned to 1 of 3 possible drug condition orders of methylphenidate and placebo<br>Mean methylphenidate dosage: N/A (modal dose at 0.3 mg/kg = 7.5 mg (range 5.0 mg to 15 mg), modal dose at 1.0 mg/kg = 27.5 mg (range 17.5 mg to 47.5 mg))<br>Administration schedule: daily single dose<br>Duration of each medication condition: 1 day<br>Washout before study initiation: 48 hours before study initiation<br>Medication-free periods between interventions: no<br>Titration period: none<br>Treatment compliance: capsules administered by project staff |
| Outcomes | **General behaviour**<br>1. Wisconsin Card Sorting Test: observer, daily, 90 minutes after treatment<br>**Non-serious adverse events**<br>1. Decreased cognitive flexibility (repetitive actions with obsessive quality)<br>2. Movement stereotypes<br>3. Facial motor tics<br>4. Topic perseveration<br>5. Excessive pre-occupation with the task at hand and persistent talkativeness: observer, during test session<br>6. Treatment-emergent side effects conducted routinely during medication trial in our laboratory<br>7. Monitored throughout sessions<br>Three children exhibited unusual side effects leading to trial termination. One exhibited hypersensitivity (skin rash, urticaria and throat clearing), and 2 became somewhat disoriented and confused and complained of odd sensations in their limbs |

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| **Notes** | Sample calculation: no<br>Ethics approval: not stated<br>**Key conclusion of study authors**<br>1. Results indicate that methylphenidate increased perseverative errors on the first assessment but decreased them on the second; clinical symptoms of perseveration occurred at both assessments. Findings suggest that methylphenidate may reduce cognitive flexibility temporarily in some children with ADHD<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Any withdrawals due to adverse events: yes; 3<br>Email correspondence with study authors: April 2014. We emailed study authors twice to ask for supplemental information/data but have not received a response |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not clear |
| Allocation concealment (selection bias) | Low risk | Double-blind, placebo-controlled design. Drug order for the first 3 test sessions was randomly assigned, and each child retained the same order for the remaining 3 sessions |
| Blinding of participants and personnel (performance bias) | Low risk | Double-blind, placebo-controlled design. Medication packaged in coloured gelatin capsules to avoid detection of dose and taste. Each child followed the same routine for every test session |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not clear |
| Incomplete outcome data (attrition bias) | High risk | Incomplete outcome data for 3 respondents with unusual side effects |
| Selective reporting (reporting bias) | Unclear risk | No information presented on numbers of participants with side effects or outcomes for data on nausea, blood pressure, etc. |
| Vested interest bias | Low risk | Research supported in part by a grant from the Canadian Psychiatric Research Foundation and a Post-Doctoral Fellowship by the Ontario Mental Health Foundation<br>Conflicts of interest: not declared |

### *Tannock 1993*

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| **Methods** | Cross-over trial with 2/3 interventions<br>1. Methylphenidate low dose<br>2. Methylphenidate high dose<br>3. Placebo<br>**Phases**<br>1. Each child in ADHD group participated in a 6-day medication trial, consisting of six 3-hour test sessions<br>2. Each child was tested on 2 separate occasions when given placebo, low-dose methylphenidate (0.3 mg/kg) and high-dose methylphenidate (1.0 mg/kg) in a randomly assigned counterbalanced sequence |

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| Participants | Number of participants screened: not stated<br>Number of participants included: methylphenidate 22, control 16. Participants were randomly assigned to 1 of 6 possible drug condition orders<br>Number of participants followed up: 22 (21 boys, 1 girl)<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-III (subtype not stated)<br>Age: mean 9.4 years (range not stated)<br>IQ: mean 105.5 (SD 11.3)<br>Methylphenidate naive: not clear: "Thus all these children would have received a trial with psychostimulants independently of this study"; "8 children had been receiving stimulant medication prior to this study")<br>Ethnicity: not stated<br>Country: Canada<br>Setting: out-patient clinic<br>Comorbidity: 55%; oppositional disorder (n = 5), conduct disorder (n = 3), emotional disorder as well as oppositional or conduct disorder (n = 4), major depression (n = 2), avoidant disorder (n = 1), separation anxiety disorder (n = 1) and learning disorder (n = 6)<br>Comedication: not clear<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Confirmed diagnosis of ADHD: Child demonstrated ≥ 3 symptoms of inattentiveness, 3 of impulsiveness and 2 of hyperactivity, with a history of these symptoms before 6 years of age, based on diagnostic interview<br>2. Diagnosis was made if the child received a Rutter B total score ≥ 9 and fulfilled any 2 of the following criteria: score ≥ 15 on the Conners' Abbreviated Teacher Questionnaire; ≥ 4 inattentive, 4 impulsive and 3 hyperactivity symptoms on the Swanson, Nolan and Pelham Scale; or score of 5 or 6 on the Rutter-B hyperactivity factor<br>**Exclusion criteria**<br>1. Wechsler Intelligence Scale for Children - Revised: score < 80 with psychosis, or with any major neurological, physical or sensory impairment |
| Interventions | Participants were randomly assigned to 1 of 6 possible drug condition orders of (dose not stated) methylphenidate and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: 6 separate medication administrations: 2 placebo, 2 low dose (0.3 mg/kg) and 2 high dose (1.0 mg/kg). First 3 test sessions were ordered randomly, than were ordered repeatedly for last 3 sessions: daily for 6 days<br>Duration of each medication condition: 3 hours<br>Washout before study initiation: 48 hours<br>Medication-free period between interventions: not clear<br>Titration period: none<br>Treatment compliance: "Medication was administered by project staff" |
| Outcomes | **Non-serious adverse events**<br>1. Blood pressure and pulse readings: before and 1 hour after ingestion<br>2. Reduced social responsivity: during each test session, observer<br>3. Intense concentration: during each test session, observer<br>4. Stereotypy: during each test session, observer |

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| **Notes** | Sample calculation: no<br>Ethics approval: not stated<br>**Key conclusions of study authors**<br>1. Results indicate that only high-dose treatment had a specific effect on focused attention, and this effect was delayed relative to the more salient but non-specific effects on overall efficiency of information processing<br>2. Task performance at high dose was related to concurrent clinical manifestations of intense concentration, but no evidence suggested that methylphenidate produced overfocusing<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: not stated<br>Email correspondence with study authors: April 2014. Emailed study authors twice for supplemental information/data but have received no response |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not stated |
| Allocation concealment (selection bias) | Low risk | Double-blind, placebo-controlled, within-participant design was used ...randomly assigned, counterbalanced sequence. Medications were prepared individually for each child and were packaged in coloured gelatin capsules to avoid detection of dose and taste |
| Blinding of participants and personnel (performance bias) | Low risk | Double-blind, placebo-controlled, within-participant design was used ...randomly assigned, counterbalanced sequence. Medications were prepared individually for each child and were packaged in coloured gelatin capsules to avoid detection of dose and taste |
| Blinding of outcome assessment (detection bias) | Unclear risk | Unclear |
| Incomplete outcome data (attrition bias) | Unclear risk | No withdrawals were noted<br>Selection bias (e.g. titration before randomisation → exclusion): no |
| Selective reporting (reporting bias) | Low risk | All outcomes reported |
| Vested interest bias | Low risk | Study funded by the Canadian Psychiatric Research Foundation and the Medical Research Council of Canada<br>Conflicts of interest: not declared |

*Tannock 1995a*

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| **Methods** | Four-day, randomised, double-blind, placebo-controlled, cross-over trial with<br>1. Three doses of methylphenidate (0.3 mg/kg, 0.6 mg/kg and 0.9 mg/kg)<br>2. Placebo<br>With initial 1-day open-label trial |

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| Participants | Number of participants screened: 28<br>Number of participants included: 28 (25 boys, 3 girls). Participants were randomly assigned to 3 doses of methylphenidate and placebo<br>Number of participants followed up: 28<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-III-R (subtype not stated)<br>Age: mean 8.9 years (range 7 to 11)<br>IQ: mean 106.5 (15.6)<br>Methylphenidate naive: 80%<br>Ethnicity: Caucasian (90%), other (10%)<br>Country: Canada<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder or conduct disorder (35%), learning disabilities (39%)<br>Comedication: not stated<br>Sociodemographics: not stated<br><br>**Inclusion criteria**<br>1. ADHD, DSM-III-R<br>**Exclusion criteria**<br>1. IQ: Wechsler Intelligence Scale for Children - Revised: score < 80<br>2. Anxiety disorder (DSM-III-R)<br>3. Major neurological, physical or sensory impairment |
| Interventions | Participants were randomly assigned to 3 doses of methylphenidate (0.3 mg/kg, 0.6 mg/kg, 0.9 mg/kg) and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: once daily<br>Duration of each medication condition: 1 day<br>Washout before study initiation: For children receiving methylphenidate before trial, washout period ≥ 48 hours before trial, with no washout between periods<br>Titration period: All children participated in an initial 1-day open trial with a 0.3 mg/kg dose of methylphenidate to ascertain tolerance, before proceeding with the double-blind, placebo-controlled trial<br>Treatment compliance: not stated |
| Outcomes | **Non-serious adverse events**<br>1. Cardiovascular function (heart rate). Radial pulse, taken for 1 minute. with the child seated, was measured 3 times during each session: immediately before medication (time 0) and again at 1 hour (time 1) and 2 hours (time 2) following administration of the oral dose. From time 0 to time 1, children were seated at a table, colouring or playing quietly with puzzles or board games: Children completed the cognitive task from time 1 to time 2 |

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| **Notes** | Sample calculation: yes<br>Ethics approval: yes; Institutional Research Ethics Board<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; 1-day open-label trial to ascertain tolerance towards medication, but all participants were analysed<br>**Key conclusions of study authors**<br>1. Results indicate that methylphenidate enhanced cognitive flexibility, although the high dose was less effective than lower doses in enhancing response inhibition<br>2. Dissociations of dose effects on cognitive function and behaviour were demonstrated: Dose-response functions for changes in behaviour were linear, whereas the function for response inhibition was U-shaped<br>Email correspondence with study authors: August 2013. We received from the first study authors supplemental information regarding drop-outs, screening and ethics approval |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomised |
| Allocation concealment (selection bias) | Low risk | All medication was prepared by the hospital pharmacy and was packaged in opaque gelatin capsules to avoid detection of dose and taste |
| Blinding of participants and personnel (performance bias) | Low risk | Children, parents, teachers and research staff were all blinded to medication conditions |
| Blinding of outcome assessment (detection bias) | Low risk | Children, parents, teachers and research staff were all blinded to medication conditions |
| Incomplete outcome data (attrition bias) | Low risk | Data from all 28 participants were analysed<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Low risk | No |
| Vested interest bias | Low risk | Medical Research Council of Canada and Health and Welfare Canada<br>Conflicts of interest: nothing to declare |

### *Tannock 1995b*

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| **Methods** | Cross-over trial with 1 interventions<br>1. Methylphenidate (0.3 mg/kg, 0.6 mg/kg, 0.9 mg/kg)<br>2. Placebo<br>Phases: washout (if applicable), baseline, trial<br>Two groups - ADHD and ADHD + anxiety - were subjected to the same trial |

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| Participants | Number of participants screened: 50<br>Number of participants included: 40 (34 boys, 6 girls). Participants were randomly assigned to 1 of 12 possible drug condition orders<br>Number of participants followed up: 40<br>Number of withdrawals: none<br>Diagnosis of ADHD: DSM-III-R (no subtype)<br>Age: mean not stated (range 7 to 11 years); ADHD mean 9.4; ADHD + anxiety mean 9.1<br>IQ: > 80<br>Methylphenidate naive: not stated<br>Ethnicity: Caucasian (90%), African American or Asian (10%)<br>Country: Canada<br>Setting: out-patient clinic<br>Comorbidity (type: overanxious 27.5%, separation anxiety 5%, overanxiety and separation anxiety 10%, avoidant disorder with overanxious traits 2.5%, ODD 55%, conduct disorder 10%)<br>Comedication: not stated<br>Sociodemographics: predominantly from middle-class families<br>**Inclusion criteria**<br>1. Meeting DSM-III-R criteria<br>2. At least 2 of the following<br>a. ≥ 15 on the Conners' Abbreviated Symptom Questionnaire<br>b. ≥ 4 inattentive, 4 impulsive and 3 hyperactive symptoms rated as "pretty much" or "very much" on Swanson, Nolan and Pelham Questionnaire<br>c. Score of 5 or 6 on the Hyperactivity factor of the Rutter Child Scales<br>**Exclusion criteria**<br>1. Full scale IQ < 80<br>2. Evidence of major neurological, physical or sensory impairment<br>3. Medical or neurological contraindications for stimulant medication<br>4. Not knowing the number facts of 10. Needing to use concrete materials (i.e. fingers) to add numbers<br>**Inclusion criteria for the ADHD + anxiety group**<br>One or more of the following<br>1. DSM-III-R criteria for overanxious, separation anxiety or avoidant disorder based on parent interview<br>2. Score > 1 SD above the mean for age and sex on the Revised Children's Manifest Anxiety Scale<br>3. Score > 1 SD for age and sex on the Trait Scale-C2 of the State-Trait Anxiety Inventory for Children<br>Children in the ADHD group did not meet any of these criteria for anxiety |
| Interventions | Participants were randomly assigned to 1 of 12 possible drug condition orders of 0.3 mg/kg, 0.6 mg/kg or 0.9 mg/kg methylphenidate and placebo<br>Mean methylphenidate dosage: 0.3 mg/kg = 8.75 (± 2.2); 0.6 mg/kg = 17.75 (± 4.2); 0.9 mg/kg = 27.25 (± 5.6)<br>Administration schedule: once per day<br>Duration of each medication condition: 1 day<br>Washout before study initiation: 48 hours when applicable<br>Medication-free period between interventions: not stated<br>Titration period: 1-day open trial on 0.3 mg/kg before proceeding to ascertain tolerance. Not stated whether initiated before/after randomisation<br>Treatment compliance: Medication was administered at the laboratory |

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| **Outcomes** | **Non-serious adverse events**<br>1. Heart rate and radial pulse, once at baseline and 3 times during each session |
| **Notes** | Sample calculation: not stated<br>Ethics approval: not stated<br>**Key conclusion of study authors**<br>1. High levels of trait anxiety in children with ADHD predict poor (but not adverse) response to methylphenidate in terms of working memory, and add to growing evidence that ADHD with anxiety constitutes a distinct and clinically meaningful subtype of ADHD<br>**Comment from review authors**<br>1. Main trial was preceded by a 1-day trial of the lowest dose to assess tolerance to methylphenidate<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; see above<br>Any withdrawals due to adverse events: no<br>Email correspondence with study authors: June 2014. Emailed study authors twice to request supplemental information/data but have received no response |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Drug order was counterbalanced and determined by random assignment, such that an approximately equal numbers of children were assigned to each of 12 possible orders |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Low risk | Active medication and placebo were prepared by the hospital pharmacy, packaged in identical opaque gelatin capsules and administered in a double-blind manner |
| Blinding of outcome assessment (detection bias) | Unclear risk | Double-blind |
| Incomplete outcome data (attrition bias) | Low risk | No drop-outs<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): 1-day open trial to assess tolerance before main trial, but no children were excluded |
| Selective reporting (reporting bias) | Low risk | All outcomes are reported |
| Vested interest bias | Low risk | Research was supported in part by the Ontario Mental Health Foundation and the National Health Research and Development Program, Health Canada |

*Taylor 1987*

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| **Methods** | Double-blind, randomised, placebo-controlled, cross-over trial with 2 arms<br>1. Methylphenidate<br>2. Placebo<br>Each treatment period lasted for 3 weeks with a washout period of 1 week planned between treatments and up-titration to optimum dosage during the 3 weeks |

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| Participants | Number of participants screened: 64<br>Number of participants included: 39. Of these, 26 had an ADHD diagnosis according to DSM-III. Participants were randomly assigned to 1 of 2 possible drug condition orders<br>Number of participants followed up: 38<br>Number of withdrawals: 1<br>Diagnosis of ADHD: DSM-III (n = 26; type not stated)<br>**The following data reflect the whole trial (n = 38)**<br>Age: mean 8.6 years (range 6 to 10)<br>IQ: all > 65; mean 93.4<br>Sex: all boys<br>Methylphenidate naive: 100%<br>Ethnicity: not stated<br>Country: England<br>Setting: out-patient clinic<br>Comorbidity: no attentive or restless behaviour, but antisocial, disruptive or aggressive in conduct (n = 6), hyperactive but not antisocial or aggressive (n = 9), with both hyperactive and disruptive behaviour (n = 23), conduct disorder (n = 7), relationship problems (n = 2) and disturbance of emotions specific to childhood (n = 3)<br>Comedication: not stated<br>Sociodemographics: 40% from broken homes<br>**Inclusion criteria**<br>1. IQ > 65<br>2. Free of autistic features<br>3. Lives in a family home, not an institution<br>4. Attending primary school<br>5. Problems assessed at the clinic as severe enough to warrant psychiatric treatment<br>6. Free of contraindications to stimulant medication<br>7. No treatment with stimulant drugs<br>8. No psychotropic drugs given for ≥ 6 months previously<br>**Exclusion criteria**<br>1. Children with severe intellectual retardation or neurological disease<br>2. Autistic and psychotic children<br>3. Pre-school children<br>4. Adolescents<br>5. Female |
| Interventions | Participants were randomly assigned to 1 of 2 possible drug condition orders of methylphenidate and placebo<br>Mean methylphenidate dosage: 9 received doses from 0.2 mg/kg to 0.5 mg/kg, 21 from 0.5 mg/kg to 0.9 mg/kg and 8 from 0.9 mg/kg to 1.4 mg/kg<br>Administration schedule: time points not stated<br>Duration of each medication condition: 3 weeks<br>Washout before study initiation: All were stimulant-naive<br>Medication-free period between interventions: 1 week<br>Titration period: A flexible dosage regimen was used after randomisation. Each child began with 5 mg daily, with dosage adjustments made at 2- to 3-day intervals. The optimum dosage was assessed for each child, in the light of clinical response and the occurrence of side effects, to a maximum of 30 mg daily<br>Treatment compliance: Compliance with medication was rated as good or very good in 89% |

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| Outcomes | **ADHD symptoms**<br>1. Conners' Teacher Rating Scale: rated at the end of each treatment period, that is, day 21<br>2. Parental Account of Childhood symptoms (PACS), hyperactivity scale: rated at the end of each treatment period, that is, day 21<br>**Serious adverse events**<br>1. No serious physical effects of medication were encountered<br>**Non-serious adverse events**<br>1. Unwanted effects of medication were assessed by using the physician's ratings of 26 possible symptoms with full physical examination, rated at the end of each treatment period, that is, day 21 |
| Notes | Sample calculation: no<br>Ethics approval: not stated<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no; all methylphenidate treatment-naive<br>**Comment from study authors (limitation)**<br>1. Long-term treatment with stimulant drugs could not be assessed in this short-term trial<br>**Key conclusion of study authors**<br>1. A good response to methylphenidate was predicted by higher levels of inattentive and restless behaviour, impaired performance on tests of attention, clumsiness, younger age and absence of symptoms of overt emotional disorder. DSM-III and ICD-9 diagnoses of "hyperactivity" were not good predictors<br>**Comments from review authors**<br>1. Long-term treatment with stimulant drugs could not be assessed in this short-term trial<br>2. Children with tics or cardiovascular disease were excluded<br>3. Demographic characteristics and mean dose include the whole sample (n = 38). However, upon receipt of correspondence from the trial author, outcomes measured included the 26 individuals diagnosed with ADHD (DSM-III)<br>4. Invetigators tested both for methylphenidate vs placebo (effects of treatment) and for end of first treatment period vs end of second treatment period (effects of occasion), as well as the interaction between treatment and occasion. "The two order groups were combined together for those measures that had shown no significant effects of test occasion or interaction of occasion with treatment. For measures which did show main or interactive effects of occasion, the two order groups were considered separately"<br>Email correspondence with trial authors: October 2013. We received from trial authors no supplemental information regarding data |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Children were randomly allocated to receive drug first or placebo first. This was carried out by pharmacy staff, who knew only the name and identifying number of each case |
| Allocation concealment (selection bias) | Low risk | Allocation was carried out by pharmacy staff, who knew only the name and identifying number of each case |
| Blinding of participants and personnel (performance bias) | Low risk | Tablets were dispensed to a trial member, who did not know what they contained and handed them to parents |
| Blinding of outcome assessment (detection bias) | Low risk | Psychiatrist supervising treatment also assessed and recorded side effects, physical findings and parents' general impressions at the end of each treatment; other assessors of outcomes were blinded to the treatment given but also to possible clues arising from physical effects of the drug. Behavioural measures were carried out independently of one another by investigators blind to results of the other tests and to teacher ratings |
| Incomplete outcome data (attrition bias) | Low risk | Data were missing for 3 children: One child had missing data on the Parental Account of Childhood Symptoms because he had been taken into care, and two children had missing data on the Conners' Teacher Rating Scale hyperactivity factor because they had been excluded from school. Method of imputation not described |
| Selective reporting (reporting bias) | Unclear risk | Not stated |
| Vested interest bias | High risk | Partially funded by grant from CIBA Ltd., which provided medicine and placebo<br>Conflicts of interest: Dr. Schachar was supported during this period by a fellowship from the Medical Research Council of Canada&& |

*Taylor 1993*

| Methods | Four-week, double-blind, cross-over trial with 3 interventions<br>1. Two different doses of methylphenidate<br>2. Placebo<br>Each medication dose/placebo was given for 1 week |
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| Participants | Number of participants screened: 57<br>Number of participants included: 32 (27 boys, 5 girls) were randomly assigned to possible drug condition orders<br>Number of participants followed up: 32<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-III-R<br>Age: mean 10.26 years (range 7.0 to 12.9)<br>IQ: mean 107 (SD 16.2; range 78 to 139)<br>Methylphenidate naive: 12 (37.5%)<br>Ethnicity: no information<br>Country: Canada<br>Setting: out-patient clinic<br>Comorbidity: no information<br>Comedication: no information<br>Sociodemographics: no information<br>**Inclusion criteria**<br>1. 7 to 12 years of age<br>2. Verbal or performance IQ ≥ 85<br>**Exclusion criteria**<br>1. No information |
| Interventions | Participants were randomly assigned to possible drug condition orders of, respectively, mean 6.72 mg (5 mg to 10 mg) and mean 11.88 mg (10 mg to 15 mg) methylphenidate and placebo<br>Administration schedule: morning and noon<br>Duration of each medication condition: 1 week<br>Washout before study initiation: none<br>Titration period: none<br>Treatment compliance: no information |
| Outcomes | **Non-serious adverse events**<br>1. Decreased appetite, trouble falling asleep, stomachache, headache, dysphoria; withdrawn, tearful, anxious, licking lips, picking at skin; facial grimacing, repetitive movements |
| Notes | Sample calculation: no information<br>Ethics approval: no information<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes<br>**Key conclusion of study authors**<br>1. Only ERPs (event-related potentials) reflected slowed processing in children with ADHD that normalised with appropriate medication<br>Email correspondence with study authors: January 2014. No supplemental information was received. We therefore have no more information on numbers of participants with non-serious adverse events |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomised. All medication and placebo testing was conducted under double-blind conditions with randomly assigned testing order |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | Active medication and placebo substances were placed in identical red and white capsules in powder form. Matched on both taste and appearance |
| Blinding of outcome assessment (detection bias) | Unclear risk | All medication and placebo testing was conducted under double-blind conditions with randomly assigned testing order, but how blinding was done was not described |
| Incomplete outcome data (attrition bias) | High risk | Selection bias: This series of 32 children with ADHD does not include an additional group of 12 children with ADHD, who after drug trials were deemed "non-responders" |
| Selective reporting (reporting bias) | High risk | Did not report adverse event data |
| Vested interest bias | Unclear risk | Not stated |

*Tervo 2002*

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| **Methods** | Triple-blind, 3-way, cross-over trial with 2 interventions<br>1. Methylphenidate at high and low doses<br>2. Placebo<br>**Phases**<br>1. High: 0.3 mg/kg b.i.d.<br>2. Low: 0.05 mg/kg b.i.d. |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 63 (49 boys, 14 girls). Participants were randomly assigned to 1 of 2 possible drug condition orders<br>Number of participants followed up: 49<br>Number of withdrawals: 14<br>Diagnosis of ADHD: DSM-IV (combined (70%), hyperactive-impulsive (16%), inattentive (5%), other (9%))<br>Age: mean 9 years 10 months (SD 2 years 10 months; range not stated)<br>IQ: not stated<br>Methylphenidate naive: not stated<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: motor dysfunction (35%)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Not stated<br>**Exclusion criteria**<br>1. Not stated |

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|---|---|
| Interventions | Participants were randomly assigned to 1 of 2 possible dose levels of immediate-release methylphenidate and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: twice daily; time points not stated<br>Duration of each medication condition: 6 days<br>Washout before study initiation: 1 day<br>Titration period: not stated<br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br>1. Conners' Parent Rating Scale: parent-rated at baseline and at end of period<br>2. Conners' Teacher Rating Scale: teacher-rated at baseline and at end of period<br>**General behaviour**<br>1. Child Behavior Checklist (CBCL): parent-rated at baseline and at end of period<br>2. Home Situations Questionnaire: parent-rated at baseline and at end of period<br>3. Teacher report form (similar to CBCL): teacher-rated at baseline and at end of period<br>4. School Situations Questionnaire: teacher-rated at baseline and at end of period<br>**Non-serious adverse events**<br>1. Side Effects Rating Scale: parent, at baseline and at end of period |
| Notes | Sample calculation: no<br>Ethics approval: no<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Comments from study authors**<br>1. A limitation of this study is that neuropsychological functioning (e.g. intellect, ability, memory, visual perceptual functioning) was not measured in all children<br>2. All children with MD had substantially impaired motor skills and "soft neurological signs" such as mixed laterality, mirror or overflow movements or choreiform movements<br>**Key conclusions of study authors**<br>1. Children with ADHD-MD were more likely to have severe ADHD combined type and other neurodevelopmental and behavioural problems<br>2. Both groups of children had a linear dose response to medication (placebo, low, high), and no evidence was found of a group-by-dose interaction or an overall group effect at home or at school<br>**Comments from review authors**<br>1. IQ not reported<br>2. Four children withdrew from the study as the result of adverse reactions - all taking high dose<br>Email correspondence with study authors: April 2013. We received from study authors the full dataset in SPSS |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomly assigned |
| Allocation concealment (selection bias) | Low risk | Only the clinical pharmacist knew the sequence of phases |
| Blinding of participants and personnel (performance bias) | Low risk | Capsules of medication and placebo were made and dispensed as described by Barkley (1988). Tablets were crushed and placed within orange opaque gelatin capsules. Capsules disguised the taste of methylphenidate and lactose placebo |
| Blinding of outcome assessment (detection bias) | Low risk | Triple-blind |
| Incomplete outcome data (attrition bias) | High risk | 14 of the 63 trials were excluded from the analysis because of inadequately completed outcome measures. Four of the 14 children did not complete the trial because of adverse reactions to medication (e.g. irritability, headache, stomachache). These children received high-dose medication in the first trial interval |
| Selective reporting (reporting bias) | Low risk | No protocol was published. All pre-specified outcomes of interest have been reported |
| Vested interest bias | Unclear risk | No conflicts of interest have been disclosed |

*Tirosh 1993a*

| | |
|---|---|
| **Methods** | 16-day, double-blind, cross-over, counterbalanced study with 2 interventions<br>1. Methylphenidate<br>2. Placebo |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 20 (16 boys, 4 girls). Participants were randomly assigned to 1 of 2 possible drug condition orders<br>Number of participants followed up: 20<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-III (ADD 30%, ADHD 70%)<br>Age: mean 9.3 years (range 7 to 12)<br>IQ: mean 102 (SD 11)<br>Methylphenidate naive: 100%<br>Ethnicity: not stated<br>Country: Israel<br>Setting: out-patient clinic<br>Comorbidity: no<br>Comedication: no<br>Sociodemographics: middle (12), upper-middle (5) and low (3) socioeconomic status of parents<br>**Inclusion criteria**<br>1. DSM-III diagnosis of ADHD<br>2. 7 to 12 years old<br>**Exclusion criteria**<br>1. Methylphenidate before study<br>2. Neurological, sensory or physical health problems |

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| **Interventions** | Participants were randomly assigned to 1 of 2 possible drug condition orders of methylphenidate and placebo<br>Methylphenidate dose range: 0.3 mg/kg to 0.5 mg/kg<br>Administration schedule: twice daily<br>Duration of each medication condition: 8 days<br>Washout before study initiation: no (participants were methylphenidate naive)<br>Titration period: no<br>Treatment compliance: Parents were asked to bring their packages of tablets back for pill count; no data |
| **Outcomes** | **ADHD symptoms**<br>1. Abbreviated Parent Rating Scale (APRS), weekly<br>2. Teacher Rating Scale (TRS), weekly |
| **Notes** | Sample calculation: no<br>Ethics approval: yes<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Funding: no funding<br>**Key conclusions of study authors**<br>1. Teacher Rating Scale: Placebo-drug difference correlated more significantly with outcome measures than did the baseline drug difference<br>2. Study underlines the validity of a multi-measure placebo/drug trial in evaluating the efficacy of methylphenidate for children with attention deficit disorder<br>Email correspondence with study authors: August 2013. Study author stated that data were discarded (Ramstad 2013d [pers comm]) |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomisation with a table of random numbers |
| Allocation concealment (selection bias) | Low risk | Look-alike placebo tablets were supplied by the hospital pharmacy and were similarly administered |
| Blinding of participants and personnel (performance bias) | Low risk | Double-blind |
| Blinding of outcome assessment (detection bias) | Low risk | Double-blind |
| Incomplete outcome data (attrition bias) | Unclear risk | No information |
| Selective reporting (reporting bias) | Unclear risk | No protocol available |
| Vested interest bias | Unclear risk | No information |

### *Tirosh 1993b*

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|---|---|
| **Methods** | Double-blind, controlled, cross-over trial with 2 interventions<br>1. Methylphenidate<br>2. Placebo |
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|---|---|
| Participants | Number of participants screened: unknown<br>Number of participants included: 11 (8 boys, 3 girls). Participants were randomly assigned to 1 of 2 possible drug condition orders<br>Number of participants followed up: 10<br>Number of withdrawals: 1<br>Diagnosis of ADHD: DSM-III (subtype not stated)<br>Age: median 9 years 8 months (range 6.9 to 12.3 years)<br>IQ: median 106 (range 92 to 118)<br>Methylphenidate naive: 100%<br>Ethnicity: not stated<br>Country: Israel<br>Setting: out-patient clinic<br>Comorbidity: none<br>Comedication: none<br>Sociodemographics: low middle class (n = 2), middle class (n = 8)<br>**Inclusion criteria**<br>1. Healthy; no neurological deficit<br>2. Living with their natural parents<br>3. Medication-naive<br>**Exclusion criteria**<br>1. Not stated |
| Interventions | Participants were randomly assigned to 1 of 2 possible drug condition orders of 0.3 mg/kg to 0.4 mg/kg methylphenidate hydrochloride (total dose 10 mg to 15 mg) and placebo<br>Mean methylphenidate dosage: 0.3 mg/kg to 0.4 mg/kg<br>Administration schedule: once daily at 7:30 AM on 6 of the 8 days. During the other 2 days, a second dose was administered at 2:00 PM<br>Duration of each medication condition: 8 days<br>Washout before study initiation: not stated<br>Medication-free period between interventions: 3 days<br>Titration period: none<br>Treatment compliance: As measured by returned package pill counts, this was rated as full compliance for the 10 children remaining in the study |
| Outcomes | **ADHD symptoms**<br>1. Conners' Teacher and Parent Rating Scale: before therapy and after each intervention<br>**Non-serious adverse events**<br>1. Sleep measurements, 10 minutes before "lights out" until morning awakening for 4 successive nights during each of the 3 respective periods |

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| **Notes** | Sample calculation: no<br>Ethics approval: not stated<br>**Key conclusions of study authors**<br>1. Results support the notion that ADHD is a centrally generated disorder attributable to hypoarousal, which subsequently stimulates motor overactivity<br>2. Methylphenidate does not appear to affect sleep patterns adversely and possibly normalises them in individuals with ADHD<br>**Comment from review authors**<br>1. No useful data<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: December 2013. We were unable to receive supplemental data from study authors because the study is 20 years old (Ramstad 2013d [pers comm]) |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | High risk | A drug-placebo sequence was used for children assigned odd numbers in the study and vice versa |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | Look-alike placebo tablets were supplied |
| Blinding of outcome assessment (detection bias) | Low risk | Investigator who analysed the data was unaware of the drug-placebo sequence |
| Incomplete outcome data (attrition bias) | Unclear risk | No information<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | No protocol available |
| Vested interest bias | Unclear risk | No information |

### *Tourette's Syndrome Study Group 2002*

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| **Methods** | Sixteen-week, multi-centre, randomised, double-blind, placebo-controlled, parallel trial to assess the efficacy of clonidine and methylphenidate for children and adolescents with ADHD and chronic tic disorder<br>Weeks 1 to 4: clonidine/placebo dose titration; week 5 to 8: addition of methylphenidate/placebo dose titration; week 9 to 16: maintenance therapy |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 136<br>Number of participants randomly assigned: methylphenidate 37, placebo 32, clonidine 34, methylphenidate + clonidine 33<br>Number of participants followed up: methylphenidate 33, placebo 25, clonidine 30, methylphenidate + clonidine 33<br>Number of withdrawals: methylphenidate 4, placebo 7, clonidine 4, clonidine + methylphenidate 4<br>Diagnosis of ADHD: DSM-IV: methylphenidate: combined 32%, hyperactive-impulsive 3%, inattentive 65%; placebo: combined 19%, hyperactive-impulsive 0%, inattentive 81%; clonidine: combined 21%, hyperactive-impulsive 3%, inattentive 76%; clonidine + |

methylphenidate: combined 33%, hyperactive-impulsive 3%, inattentive 64%

Mean age: methylphenidate 10.7 years (SD 2.0); placebo 9.7 years (SD 1.8); clonidine 9.7 years (SD 1.8); clonidine + methylphenidate 10.6 years (SD 1.9). Total age range 7 to 14

Sex: methylphenidate 34 boys, 3 girls; placebo 29 boys, 3 girls; clonidine 29 boys, 5 girls; clonidine + methylphenidate 24 boys, 9 girls

Stimulant-naive: 42%

Ethnicity: methylphenidate 81% Caucasian; placebo 94% Caucasian; clonidine 94% Caucasian; clonidine + methylphenidate 85% Caucasian

Country: USA

Setting: out-patient clinic

Comorbidity: tic disorder diagnosis 100%; primarily obsessive-compulsive disorder (OCD) and oppositional defiant disorder (ODD). Furthermore, conduct disorder, generalised anxiety disorder and major depressive disorder. Methylphenidate: obsessive-compulsive disorder (11%), oppositional defiant disorder (33%). Placebo: obsessive-compulsive disorder (22%), oppositional defiant disorder (41%). Clonidine: obsessive-compulsive disorder (15%), oppositional defiant disorder (48%). Clonidine + methylphenidate: obsessive-compulsive disorder (16%), oppositional defiant disorder (31%)

Comedication: not stated

IQ: > 70

Sociodemographics: not stated. Participant groups were similar, except that participants assigned to methylphenidate (alone or in combination with clonidine) are approximately 1 year older, present a higher proportion of pubertal cases, show underrepresentation of the inattentive subtype of ADHD (and overrepresentation of the combined subtype) and have lower baseline Conners' Abbreviated Symptom Questionnaire (ASQ)-Teacher scores. A higher proportion of girls was found in the combined treatment group

**Inclusion criteria**

1. DSM-IV for ADHD
2. Designated teacher in daily direct contact with the participant had to indicate the presence of a sufficient number of ADHD symptoms (rated as "pretty much" or "very much") in the classroom setting using the Disruptive Behavior Disorders Rating Scale (updated to DSM-IV) to meet DSM-IV criteria; and had to rate the severity of ADHD symptoms above specified cutoff scores (boys: grade 2 to 3 = 10, grade ≥ 4 = 9; girls: grade 2 to 3 = 7, grade ≥ 4 = 6) on the Iowa Conners' Teacher Rating Scale
3. Investigator’s rating of global functioning on the Child-Global Assessment Scale (C-GAS) had to be 70 (indicating difficulty in ≥ 1 area, such as school)
4. DSM-IV for Tourette's disorder, chronic motor tic disorder or chronic vocal tic disorder

**Exclusion criteria**

1. Secondary tic disorder (tardive tics, neuroacanthocytosis, Huntington disease)
2. Major depression, pervasive developmental disorder, autism, psychosis, anorexia nervosa, bulimia, serious cardiovascular or other medical disorder that would preclude the safe use of methylphenidate or clonidine, impaired renal function, pregnancy
3. Mental retardation
4. The following cardiac conditions: prolonged QTc interval (> 440 milliseconds), high-grade ventricular ectopy, AV block > 1 degree, bundle branch block, intraventricular conduction block (100 milliseconds), pacemaker rhythm or heart rate < 60 on the electrocardiogram, cardiomyopathy, complex heart disease, aortic or pulmonary stenosis, family history of long QT syndrome, cardiomyopathy or premature sudden death (age 45 years), history of syncope and blood pressure < 2 SD from age- and sex-adjusted mean
5. Other medications for treatment of ADHD, tics or other associated behavioural symptoms. Any such treatment had to be discontinued ≥ 6 weeks (2 weeks for methylphenidate) before enrolment

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| Interventions | Participants were randomly assigned to methylphenidate (Ritalin; Novartis) alone, clonidine alone, clonidine + methylphenidate or placebo<br><br>Methylphenidate dosage: methylphenidate alone 25.7 mg/d, methylphenidate + clonidine 26.1 mg/d<br><br>Administration schedule: 2 to 3 times daily<br><br>Duration of intervention: 12 weeks (4-week titration of methylphenidate, 8-week maintenance phase)<br><br>Titration period: 4-week initial dose titration period for clonidine, after which came 4-week dose titration for methylphenidate. Both titration periods took place after randomisation<br><br>Treatment compliance: Pill count monitored compliance |
| Outcomes | **ADHD symptoms**<br><br>1. ADHD Conners' Abbreviated Symptom Questionnaire for Teachers (ASQ-Teacher): rated at baseline and at week 16<br>2. Iowa Conners' Teacher Rating Scale: rated at baseline and at week 16<br>3. Conners' Abbreviated Symptom Questionnaire for Parents (ASQ-Parent): rated at baseline and at weeks 8, 12 and 16<br><br>**General behaviour**<br><br>1. Iowa Conners' Teacher Rating Scale: rated at baseline and at week 16<br><br>**Quality of life**<br><br>1. Children's Global Assessment Scale: rated by site investigator at baseline and at weeks 8, 12 and 16<br><br>**Non-serious adverse events**<br><br>1. Yale Global Tic Severity Scale (YGTSS): rated by site investigator at weeks 8, 12 and 16<br>2. Tic Symptom Self-Report Scale (TSSR): parent/participant- and teacher-rated at weeks 8, 12 and 16 (teacher ratings only at week 16)<br>3. Global Tic Rating Scale: parent/participant- and teacher-rated at weeks 8, 12 and 16 (teacher ratings only at week 16)<br>4. Vital signs, ECG: rated at weeks 8, 12 and 16<br>5. Side Effects Rating Scale: rated at weeks 8, 12 and 16 (teacher ratings only at week 16)<br>6. Independent safety monitoring committee, consisting of child psychiatrist, paediatric cardiologist, paediatrician and statistician; reviewed data regarding adverse events throughout the study |

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| **Notes** | Sample calculation: yes; 120 participants<br>Ethics approval: yes; the protocol was approved by the institutional review board at each site<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Comment from study authors**<br>1. Our study did exclude participants with known cardiac problems, so the safety of combined clonidine and methylphenidate in this group was not addressed<br>**Key conclusions of study authors**<br>1. Our study indicates that prior concerns that methylphenidate worsens tics and that the drug should be avoided in patients with tics may be unwarranted<br>2. The most effective treatment for ADHD in our trial was the combination of clonidine and methylphenidate, although the incremental benefit of adding clonidine to methylphenidate came at the expense of additional side effects, particularly sedation<br>**Comments from review authors**<br>1. Data extracted from week 4 to week 16 (from when methylphenidate was introduced to participants)<br>2. Not able to use study data in our analyses |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computer-generated randomisation. Stratification by centre (investigator) and sexual maturity status (prepubertal: Tanner stage I to II; pubertal: Tanner stage III to V) Blocking was used to ensure approximate balance among treatment groups within each stratum |
| Allocation concealment (selection bias) | Low risk | Sealed envelopes that contained participants' treatment assignments |
| Blinding of participants and personnel (performance bias) | Low risk | Blinded: participants, clinicians, data collectors, outcome assessors, data analysts, data safety and monitoring committee, manuscript writers |
| Blinding of outcome assessment (detection bias) | Low risk | Only the programmer in the Biostatistics Center who generated the plan and the pharmacist in the Pharmacy Center who packaged and labeled the drug were aware of treatment assignments |
| Incomplete outcome data (attrition bias) | Low risk | Primary statistical analyses were performed according to the ITT principle and were based on all randomly assigned participants, as randomised. For analysis of outcome variables for efficacy, if a participant was missing a response at a particular visit, the last available observation for that participant was carried forward and imputed for that visit<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): no |
| Selective reporting (reporting bias) | Low risk | No |
| Vested interest bias | Unclear risk | Vested interest: the National Institute of Neurological Disorders and Stroke, the General Clinical Research Center, the National Center for Research Resources, the Tourette Syndrome Association<br>Boeringer Ingelheim Inc. (particularly Dr. Virgil Dias), for supplying clonidine and matching placebo; Bausch and Lomb, Inc., for supplying small gifts for our study participants<br>Conflicts of interest: none declared |

*Tucker 2009*

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| **Methods** | Multi-centre, open-label RCT including behaviour treatment as cointervention with 2 arms<br>1. Extended-release methylphenidate and behavioural treatment<br>2. Behavioural treatment |
| **Participants** | Number of participants screened: 142<br>Number of participants included: 109<br>Number of participants followed up: 104 (66 boys, 38 girls)<br>Number of withdrawals: 5<br>Diagnosis of ADHD: DSM-IV (subtypes not described)<br>Age: mean 8.4 years (range 6 to 12)<br>IQ: not stated; all age-appropriate cognitive functioning<br>Methylphenidate naive: 100%<br>Ethnicity: Caucasian (73.1%), African American (24.0%), other (2.9%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: none<br>Comedication: no<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. DSM-IV diagnosis of ADHD<br>2. Age-appropriate cognitive functioning<br>**Exclusion criteria**<br>1. Previous exposure to methylphenidate or any amphetamine-based medication<br>2. Positive urine drug screen<br>3. Clinically significant abnormality in the screening assessment (physical exam, vital signs, laboratory tests)<br>4. Cardiac abnormality<br>5. History of seizures or schizophrenia; current diagnosis of mood disorder or anxiety disorder |
| **Interventions** | Participants were randomly assigned to extended-release methylphenidate plus behavioural treatment or to behavioural treatment alone<br>Mean methylphenidate dosage: not stated<br>Administration schedule: once daily<br>Duration of intervention: 3 months<br>Titration period: initiated after randomisation. Methylphenidate was started at 10 mg/d and could be increased weekly in intervals of 10 mg/d to a maximum of 60 mg/d. Methylphenidate was administered to achieve the desired clinical effect with minimum or no side effects<br>Treatment compliance: not stated |
| **Outcomes** | **ADHD symptoms**<br>1. Conners' ADHD/DSM-IV Scales for Parents: measured at baseline and at end of treatment<br>**Non-serious adverse events**<br>1. Investigating for potential genotoxic effects: No significant differences were found<br>2. Chromosomal aberrations (CAs), including micronuclei (MN) and sister chromatid exchanges (SCEs), in cultured peripheral blood lymphocytes. Blood samples were obtained from all participating patients for evaluation of cytogenetic status at baseline and after 3 months of treatment. These data are not used in the review |

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| **Notes** | Sample calculation: yes<br>Ethics approval: yes; approved by the ethics committees for all 17 study centres<br>**Key conclusion of study authors**<br>1. These findings support the notion that methylphenidate does not induce chromosomal alterations nor other types of genetic damage in children treated for ADHD<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no; all participants were Methylphenidate naive<br>Email correspondence with study authors: December 2013 and January 2014. Not able to contact study authors |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomised; no further description |
| Allocation concealment (selection bias) | Unclear risk | Randomisation was stratified by age group (6 to 8 years and 9 to 12 years) and by centre |
| Blinding of participants and personnel (performance bias) | Unclear risk | Not stated |
| Blinding of outcome assessment (detection bias) | Low risk | Evaluation of cytogenetic damage by blinded slide readers |
| Incomplete outcome data (attrition bias) | High risk | Outcome data reported for 68 of 109 randomly assigned participants |
| Selective reporting (reporting bias) | Unclear risk | No protocol identified |
| Vested interest bias | High risk | This work was funded by Novartis Pharmaceuticals Corporation<br>Conflicts of interest: Some study authors were employed by Novartis (5 of 8 had a Novartis email address) |

### *Ullmann 1985*

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|---|---|
| **Methods** | Eight-week, cross-over trial<br>1. Three doses of methylphenidate (0.3 mg/kg, 0.5 mg/kg, 0.8 mg/kg)<br>2. Placebo<br>**Two phases**<br>1. Phase 1: 4-week fixed increase in methylphenidate dose<br>2. Phase 2: 4-week randomised, cross-over trial<br>The trial was conducted over 3 years |

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|---|---|
| Participants | Number of participants screened: not stated<br>Number of participants included: 86. Participants were randomly assigned to 3 doses of methylphenidate and placebo<br>Number of participants followed up: 86 (67 boys, 19 girls)<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-III (ADD (15.1%), ADD-H (70.9%), other (14.0%))<br>Age: mean 8.6 years (SD 1.8; range not stated)<br>IQ: > 70<br>Methylphenidate naive: not stated<br>Ethnicity: African American (17.4%), other (82.6%)<br>Country: USA<br>Setting: not stated<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. ADHD diagnosis according to DSM-III<br>**Exclusion criteria**<br>1. Not described |
| Interventions | Participants were randomly assigned to different doses of methylphenidate (0.3 mg/kg, 0.5 mg/kg and 0.8 mg/kg) and placebo<br>Administration schedule: once daily, before school<br>Duration of each medication condition: 1 week<br>Washout before study initiation: dose taken in the morning to the next day's dose<br>Titration period: 4 weeks<br>Treatment compliance: "compliance were probably high" |
| Outcomes | **ADHD symptoms**<br>1. ADD/H Comprehensive Teacher Rating Scale: completed by teachers on a weekly basis, on the last day before treatment switching |
| Notes | Sample calculation: *n*o information<br>Ethics approval: *n*o information<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Comment from study authors**<br>1. Order effects were non-significant, that is, ratings were similar for the first and second weeks on each dose, regardless of the order in which doses were given<br>**Key conclusion of study authors**<br>1. Results from the study show that methylphenidate has a major effect in improving attention and is helpful in decreasing activity levels but often has only a minor effect on deficient social skills and oppositional (aggressive) behaviour<br>Email correspondence with study authors: not able to find first or second study author's contact information; therefore not able to request supplemental data necessary for meta-analyses |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Random assignment |
| Allocation concealment (selection bias) | High risk | No description; only "methylphenidate in opaque capsules" |
| Blinding of participants and personnel (performance bias) | High risk | No description |
| Blinding of outcome assessment (detection bias) | Low risk | Teacher rating under blinded conditions |
| Incomplete outcome data (attrition bias) | Low risk | Data were pooled for a total of 86 participants<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | Unable to obtain protocol |
| Vested interest bias | Unclear risk | National Institutes of Mental Health (NIMH). Ciba-Geigy provided medication and placebo<br>Conflicts of interest: no information |

*Ullmann 1986*

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|---|---|
| Methods | Double-blind, cross-over trial in which participants were randomly assigned to the following conditions<br>1. Three different doses of methylphenidate (0.3 mg/kg, 0.5 mg/kg and 0.8 mg/kg)<br>2. Placebo |
| Participants | Number of participants screened: not stated<br>Number of participants included: 118. Participants were randomly assigned to 3 different doses of methylphenidate and placebo<br>Number of participants followed up: 118 (92 boys, 26 girls)<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-III (subtype not stated)<br>Age: mean 8.6 years (range 6 to 14)<br>IQ: > 70<br>Methylphenidate naive: not stated<br>Ethnicity: Caucasian (81.4%), African American (18.6%)<br>Country: USA<br>Setting: school setting and out-patient clinic<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Diagnosis of ADHD<br>**Exclusion criteria**<br>1. None mentioned |

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|---|---|
| Interventions | Participants were randomly assigned to 3 different doses of methylphenidate (0.3 mg/kg, 0.5 mg/kg and 0.8 mg/kg) and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: not stated<br>Duration of each medication condition: 1 week<br>Washout before study initiation: no information<br>Titration period: none<br>Treatment compliance: excellent compliance in all but a few children |
| Outcomes | **ADHD symptoms**<br>1. ADD/H Comprehensive Teacher Rating Scale: rated by teachers at the end of each school week<br>**Non-serious adverse events**<br>1. Teacher Checklist: rated by teachers at the end of each school week<br>Unable to obtain data on adverse events, as could not locate contact details of the first or second study author (see notes) |
| Notes | Sample calculation: no<br>Ethics approval: no information<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Key conclusion of study authors**<br>1. Double-blind placebo evaluation of children with ADD can and should be done by practitioners to avoid medicating children who are responding to non-specific effects of drugs<br>**Comment from study authors (on side effects)**<br>1. Very few children were reported completely free of adverse effects; however, these were, on the whole, mild effects. In fact, a slightly higher proportion of children were reported to show adverse psychological effects at baseline (0.60) and on baseline (0.53) than on medication (0.46), but these differences were not significant<br>**Comment from review authors**<br>1. Used data from MPH responders in our analyses, which yielded a highly biased result<br>Email correspondence with study authors: not able to find first or second study author's contact information; therefore not able to obtain additional data (e.g. data (table) on adverse effects) from study authors |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No information |
| Allocation concealment (selection bias) | Low risk | Daily doses of methylphenidate or placebo were placed in gelatin capsules to disguise taste and dose differences; medication for each week was packaged in a dated envelope |
| Blinding of participants and personnel (performance bias) | Low risk | Children, parents and teachers were blinded to dose order, as was the assistant who recorded data sent in by the teachers |
| Blinding of outcome assessment (detection bias) | Low risk | Children, parents and teachers were blinded to dose order, as was the assistant who recorded data sent in by the teachers |
| Incomplete outcome data (attrition bias) | Low risk | No incomplete outcome data<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | No protocol |
| Vested interest bias | Unclear risk | Supported in part by a National Institute of Mental Health (NIMH) grant. Ciba-Geigy provided medication and placebo<br>Conflicts of interest: not declared |

*Urman 1995*

| Methods | Double-blind, placebo-controlled, within-participant (cross-over) trial looking at cardiovascular effects of methylphenidate (0.3 mg/kg, 0.6 mg/kg and 0.9 mg/kg) doses at baseline and after 60 and 120 minutes post methylphenidate challenge in 2 groups of participants with ADHD<br>1. ADHD without anxiety<br>2. ADHD with anxiety |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 63 (58 boys, 5 girls)<br>Number of participants followed up: 63 (ADHD without anxiety 34, ADHD with anxiety 29)<br>Number of withdrawals: not stated<br>Diagnosis of ADHD: DSM-III-R (but "82% of the ADHD and 93% of the ADHD/ANX group" would meet the DSM-IV criteria for a diagnosis of ADHD combined type)<br>Age: ADHD without anxiety, mean 9.1 years (SD 1.3; range 6 to 12); ADHD with anxiety, mean 8.7 years (SD 1.4) (overall range 6 to 12)<br>IQ: not stated<br>Methylphenidate naive: 63 (100%)<br>Ethnicity: Caucasian (90%), "African or Asian descent" (10%)<br>Country: Canada<br>Setting: not stated<br>Comorbidity: ADHD group: oppositional defiant disorder (14; 42%), conduct disorder (5; 15%); ADHD with anxiety group: oppositional defiant disorder (11; 38%), conduct disorder (8; 28%). Also, in the ADHD with anxiety group, 3 met the DSM-III criteria for overanxious disorder, 2 met criteria for separation anxiety disorder and 5 met criteria for both overanxious and separation anxiety disorders)<br>Sociodemographics: "The children tended to come from middle-class families"<br>**Inclusion criteria**<br>ADHD with anxiety group<br>1. T score ≤ 1 SD above the mean for age and sex on both the RCMAS and the Trait Scale of the STAIC<br>ADHD without anxiety group<br>1. T score > 1 SD above the mean for age and sex on the RCMAS and/or the Trait Scale of the STAIC<br>2. "The children could also meet diagnostic criteria for any anxiety disorder based on the parent interview"<br>**Exclusion criteria**<br>ADHD without anxiety group<br>1. "Any child who scored within this range but met diagnostic criteria for any anxiety disorder on the basis of parent diagnostic interview was excluded from the analysis" |
| Interventions | Participants were randomly assigned to 1 of 4 possible drug condition orders of placebo and methylphenidate (0.3 mg/kg, 0.6 mg/kg or 0.9 mg/kg), given once daily over a 4-day period. Dosage was based on a child's body weight to the nearest 2.5 mg. Children followed the same routine for every test session with pre-methylphenidate measurements and with measurements at 60 minutes and again at 120 minutes after taking methylphenidate<br>Mean methylphenidate dosage: not stated<br>Duration of each medication condition: once daily, administered over a 4-day period - each medication condition given once to each child<br>Washout before study initiation: All were methylphenidate naive<br>Medication-free period between interventions: not stated<br>Treatment compliance: "Any child with missing data for a particular measure was excluded from the analysis of that measure", but study authors did not indicate the overall quantity of missing data. "Medication was administered by a research nurse" |
| Outcomes | **Non-serious adverse events**<br>1. Blood pressure (systolic and diastolic)<br>2. Heart rate (radial pulse measured for 60 seconds) |

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| Notes | Sample calculation: no information<br>Ethics approval: no information<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: not stated<br>**Comment from study authors**<br>1. From a clinical perspective, stimulant-related increases in heart rate and blood pressure in both groups of children with ADHD were modest and generally of little clinical concern. Nonetheless, the present findings of an exaggerated cardiovascular response to methylphenidate in the ADHD with anxiety group should alert clinicians to the possibility of a differential medication response in anxious ADHD children<br>**Key conclusions of study authors**<br>1. This study yielded 2 major findings. First, it demonstrated that baseline cardiovascular function did not differ between children with ADHD and children with ADHD and anxiety. Second, it revealed the presence of an exaggerated diastolic blood pressure response to methylphenidate in children with ADHD and anxiety<br>2. Data from the present study add to growing evidence that children with ADHD and anxiety constitute a distinct subgroup of children with ADHD. Moreover, the exaggerated response of children with ADHD and anxiety to methylphenidate suggests the presence of abnormal regulation of norepinephrine (NE) function in this group, compared with that observed in the anxiety disorder population<br>**Comments from review authors**<br>1. Inadequate description of method for blood pressure and heart rate measurement<br>2. Measurement of heart rate was presumably carried out by palpating radial pulse - pulse oximetry or ECG would produce more reliable results |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "The order of medications was counterbalanced and determined by random assignment such that an approximately equal number of children received each dose on a given day in the trial" |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | "All medication was prepared by the hospital pharmacy and packaged in opaque gelatin capsules, to avoid detection of dose and taste"; "Children, parents and research staff were blind to the medication conditions" |
| Blinding of outcome assessment (detection bias) | Low risk | "Medication was administered by a research nurse who was blind to children's medication condition and classification of anxiety" |
| Incomplete outcome data (attrition bias) | Unclear risk | Not stated<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | Not stated |
| Vested interest bias | Low risk | This work was supported in part by funds from the Medical Research Council of Canada and the Research Institute of the Hospital for Sick Children<br>Conflicts of interest: not declared |

*Van der Meere 1999a*

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| **Methods** | Seven-week, randomised, double-blind, placebo-controlled, parallel-group trial with 3 arms<br>1. Methylphenidate<br>2. Placebo<br>3. Clonidine |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 72 (62 boys, 10 girls)<br>Number of participants randomly assigned: methylphenidate 24, placebo 24, clonidine 24<br>Number of participants followed up in each arm: methylphenidate 23, placebo 24<br>Number of withdrawals in each arm: methylphenidate 1, placebo 0<br>Diagnosis of ADHD: DSM-III-R (subtype not stated)<br>Age: mean 8.8 years (range 7 to 12)<br>IQ: > 70<br>Methylphenidate naive: 100%<br>Ethnicity: mainly Caucasian<br>Country: the Netherlands<br>Setting: out-patient clinic<br>Comorbidity: conduct disorder (11%), oppositional defiant disorder (33%), depressive disorder (3%), overanxious disorder (1%), dysthymia (3%), generalized tonic-clonic seizures (1%), ventricular septal defect (1%), congenital hypothyroidism (1%), precocious puberty (1%), deaf in right ear (1%), atresia in 1 ear (1%)<br>Comedication: yes; for participants who had diseases that required it, for example, hypothyroidism<br>Sociodemographics: 44% from lower socioeconomic families<br>**Differences between groups**<br>1. No significant differences in age and IQ were noted between the 2 groups<br>**Inclusion criteria**<br>1. Boys and girls<br>2. 6 to 15 years of age<br>3. IQ > 70<br>4. Living in a family home and attending school<br>5. DSM-III-R diagnosis of ADHD, ADHD symptoms impeding development and psychological/educational treatments with insufficient effect<br>6. No earlier use of stimulant drugs or clonidine and no psychoactive medications of any kind in the last 6 months<br>7. No medical contraindications<br>8. No important changes expected for the course of the trial<br>9. Iit was considered clinically meaningful by both parents and the attending physician to try "hyperactivity medication"<br>**Exclusion criteria**<br>1. Additional psychoactive drugs during the trial<br>2. Pervasive developmental disorder or tic disorder. These participants were included in other trial groups |

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| Interventions | Participants were randomly assigned to methylphenidate, placebo or clonidine<br>Total oral daily methylphenidate dosage: 0.06 mg/kg<br>Mean of the absolute methylphenidate dose: 9.85 mg (2.26)<br>Administration schedule: breakfast and lunchtime<br>Duration of intervention: 7 weeks<br>Titration: no, but dosage adjustments were made/allowed during first weeks<br>Titration period: none<br>Treatment compliance: maintained and checked by instructions (both oral and written) to both parents and child, and by counting tablets remaining at the end of treatment. Only 1 participant in the methylphenidate group showed poor compliance |
| Outcomes | **ADHD symptoms**<br>1. Conners' Teacher Rating Scale: baseline and at week 7<br>**General behaviour**<br>1. Parent and Teacher Versions of the abbreviated Groninger Behaviour Observation Scale (GOO and GBO, respectively): baseline and at weeks 3, 5 and 7<br>2. Parent and Teacher Versions of the abbreviated Groninger Behaviour Checklists (GGGS and GGBS, respectively): baseline and at week 7<br>3. GPO rating: baseline and at week 7<br>**Non-serious adverse events**<br>1. Parent ratings of drowsiness, insomnia, decreased appetite, nausea, headache, nervousness, motor restlessness, feelings of dizziness, dry mouth, nightmares, apathy, irritability and "other complaints"<br>2. Child and parents were asked about all kinds of physical and behavioural complaints or changes at study visits |
| Notes | Sample calculation: yes (≥ 15 participants in each group)<br>Ethics approval: yes<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Key conclusion of study authors**<br>1. We concluded that the state regulation problem in ADHD is resistant to methylphenidate and clonidine<br>Email correspondence with study authors: September 2013. We obtained supplemental information regarding a publication with information about randomisation and supplemental data |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The statistician sent the randomisation list to the pharmacist. Participants were then randomly assigned by a research pharmacist. To ensure blinding, pharmacists applied randomisation blocks at random at a length of 2 or 4 participants. Methylphenidate and matching placebos were used |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | Teacher, parent, clinician, child and experimenter were blind to treatment conditions |
| Blinding of outcome assessment (detection bias) | Low risk | Teacher, parent, clinician, child and experimenter were blind to treatment conditions |
| Incomplete outcome data (attrition bias) | Low risk | ITT<br>Selection bias: no, but dosage adjustments were made for several participants because of annoying adverse events |
| Selective reporting (reporting bias) | Low risk | No |
| Vested interest bias | High risk | This study was supported by grants from the Sophia Foundation for Medical Research and Boehringer Ingelheim BV, the Netherlands |

*Wallace 1994*

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| **Methods** | Double-blind, single-participant, randomised, cross-over trial<br>1. Methylphenidate<br>2. Placebo<br>Conducted in 11 hospitalised children with ADHD |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 11. Participants were randomly assigned to 1 of 2 conditions: methylphenidate and placebo<br>Number followed up: 11<br>Sex: not reported<br>Number of withdrawals: 0<br>Diagnosis of ADHD: DSM-III-R (subtype not described)<br>Age: mean 9 years 5 months (range 4 to 13 years)<br>IQ: not stated<br>Methylphenidate naive: not stated<br>Ethnicity: not stated<br>Country: USA<br>Setting: hospital/out-patient clinic<br>Comorbidity type: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Children diagnosed with ADHD who were hospitalised at a psychiatric hospital<br>**Exclusion criteria**<br>1. Not stated |

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| Interventions | Participants were randomly assigned to methylphenidate and placebo on a daily basis<br>Mean methylphenidate dosage: not stated<br>Administration schedule: daily<br>Duration of each medication condition: methylphenidate 2 to 7 days, placebo 3 to 6 days<br>Washout before study initiation: not described<br>Medication-free period between interventions: none<br>Titration period: Optimal dose was based on maximal effectiveness and minimal side effects, but this appears to reflect daily response to methylphenidate<br>Treatment compliance: not described |
| Outcomes | **ADHD symptoms**<br>1. Abbreviated Conners' Teacher Rating Scale (15-item): rated by teachers and by day and night nursing staff<br>**Serious adverse events**<br>1. Side effects mentioned but not reported<br>**Non-serious adverse events**<br>1. Side effects mentioned but not reported |
| Notes | Sample calculation: not stated<br>Ethics approval: not stated<br>**Comment from study authors**<br>1. Assigning highly consistent rates would reduce variance in measurements<br>**Key conclusions of study authors**<br>1. n-of-1 trial is useful for evaluating the effectiveness of methylphenidate in individual patients with ADHD<br>2. Short duration of MPH action allows for multiple cross-over trials over a brief time<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes<br>**Comment from review authors**<br>1. Data are not reported in a suitable form for meta-analysis; therefore we could use no data from this study<br>Email correspondence with study authors: We could find no contact information; therefore, we could not get additional data through personal email correspondence with study authors |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Sequence was determined by "coin toss method" |
| Allocation concealment (selection bias) | Unclear risk | Allocation concealment not described |
| Blinding of participants and personnel (performance bias) | Unclear risk | "After completion of each trial, the treatment code was broken", but it was not clear whether the psychiatry physician and the fellow who made the decision to cease methylphenidate were blinded |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not stated |
| Incomplete outcome data (attrition bias) | High risk | All data appear to have been reported, but methylphenidate was discontinued on the basis of results; therefore, data collection did not continue for some participants |
| Selective reporting (reporting bias) | Unclear risk | Protocol not identified |
| Vested interest bias | Unclear risk | Veterans Administration Medical Center, Vermont<br>Conflicts of interest: not declared |

### *Wallander 1987*

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| **Methods** | Double-blind, placebo-controlled, cross-over trial with 3 interventions<br>1. Methylphenidate 0.3 mg/kg<br>2. Methylphenidate 0.6 mg/kg<br>3. Placebo |
| **Participants** | Number of participants screened: 28 (20 boys, 8 girls)<br>Number of participants included: not clear. Participants were randomly assigned to 1 of possible drug condition orders<br>Number of participants followed up: unclear<br>Number of withdrawals: unclear<br>Diagnosis of ADHD: DSM-III (subtype not stated)<br>Age: mean 8.4 years (range 6 to 12)<br>IQ: mean 79.64<br>Methylphenidate naive: 28 (100%)<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic and in-patient ward<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: 3.52 (Hollingshead-Redlich Index)<br>**Inclusion criteria**<br>1. Meeting DSM-III criteria for the diagnosis of ADHD, as assessed by an experienced psychiatrist and paediatrician<br>2. Scoring 2 SD above the mean for age and sex on both hyperactivity and distractibility factors of the Conners' Teacher Rating Scale<br>3. Naive to stimulant medication<br>**Exclusion criteria**<br>1. No information |

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| **Interventions** | Participants were randomly assigned to 1 of the possible drug condition orders of methylphenidate (0.3 mg/kg and 0.6 mg/kg) and placebo<br>Mean methylphenidate dosage: no information<br>Administration schedule: twice a day, 8:30 AM and noon<br>Duration of each medication condition: 12 days for in-patients and 19 days for out-patients (mean 15.25 days)<br>Washout before study initiation: none<br>Medication-free period between interventions: 68 hours<br>Titration period: none<br>Treatment compliance: no information |
| **Outcomes** | **General behaviour**<br>1. Oppositional behaviour |
| **Notes** | Sample calculation: none<br>Ethics approval: no information<br>**Key conclusions of study authors**<br>1. Results indicate no change in social behaviours, as participants decreased their display of problem behaviours as a function of stimulants<br>2. Peers and teachers responded and attendees less to them, however, when they received stimulants as compared with placebo<br>**Comment from review authors**<br>1. Data could not be used in meta-analyses because some were missing<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: December 2013. No supplemental information available |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Receiving interventions in counterbalanced orders |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Unclear risk | No information |
| Blinding of outcome assessment (detection bias) | Unclear risk | No information |
| Incomplete outcome data (attrition bias) | Unclear risk | Agreement of 90% across all categories had to be reached with this validity observer<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | Protocol not identified |
| Vested interest bias | Low risk | Funded in part by Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) grants and the University of Southern California Faculty Research and Innovation Fund<br>Conflicts of interest: not declared |

***Waxmonsky 2008***

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| **Methods** | Nine-week therapeutic summer camp consisting of a cross-over trial with 4 interventions<br>1. Placebo<br>2. Methylphenidate 0.15 mg/kg t.i.d.<br>3. Methylphenidate 0.3 mg/kg t.i.d.<br>4. Methylphenidate 0.6 mg/kg t.i.d.<br>Varied daily within a cross-over design of 3 intensities of behaviour modification therapy<br>1. No<br>2. Low<br>3. High<br>Each lasted 3 weeks |

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| Participants | Number of participants screened: 106 participants in the 2003 and 2004 Summer Treatment Program (University of Buffalo)<br><br>Number of participants included: 101. ADHD subgroup 33, ADHD + severe mood dysregulation (SMD) subgroup 68<br><br>Number of participants followed up: 99<br><br>Number of withdrawals: 2<br><br>Diagnosis of ADHD: DSM-IV (combined (92%), hyperactive-impulsive (not stated), inattentive (not stated))<br><br>Age: mean 8.5 years (range 5 to 12)<br><br>IQ: mean105<br><br>Sex: 82 boys, 19 girls<br><br>Methylphenidate naive: not stated<br><br>Ethnicity: predominantly Caucasian<br><br>Country: USA<br><br>Setting: out-patient clinic (Summer Treatment Program)<br><br>Comorbidity: oppositional defiant disorder (54%), conduct disorder (12%)<br><br>Comedication: not stated<br><br>Sociodemographics: predominantly middle class<br><br>**Inclusion criteria**<br><br>1. 5 to 12 years of age<br>2. Participants were required to stop all psychotropic medication 1 week before intake<br>3. DSM-IV diagnosis of ADHD<br>4. ADHD-related impairment in ≥ 2 realms according to Parent and Teacher Versions of the Impairment Rating Scale (IRS)<br>5. IQ > 80<br>6. Subgroups<br>   a. ADHD: not meeting National Institutes of Mental Health criteria for severe mood dysregulation<br>   b. ADHD plus severe mood dysregulation: meeting National Institutes of Mental Health criteria for severe mood dysregulation, and having Young Mania Rating Scale (YMRS) score ≥ 12 based on the last month's behaviour and Conners' Global Index (CGI) mania severity score ≥ 3<br><br>**Exclusion criteria**<br><br>1. History of seizures or other neurological problems<br>2. Medical history that would involve considerable risk in taking stimulant medication<br>3. History or concurrent diagnosis of any of the following disorders: pervasive developmental disorder, schizophrenia or other psychotic disorders, sexual disorder, organic mental disorder or eating disorder<br>4. Documented serious adverse reaction to methylphenidate<br>5. Significant developmental delays or autistic spectrum illness<br>6. Active use of psychotropic medication for disorders besides ADHD, including use of antidepressants or mood-stabilising medications<br>7. Meeting full criteria for the narrow-phenotype criteria of bipolar disorder or in need of urgent psychiatric treatment (active suicidal ideation). Participants newly identified with major depressive disorder or bipolar disorder on the Diagnostic Interview Schedule for Children were directly assessed by an M.D.- or Ph.D.-level clinician |

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| Interventions | Participants attended a Summer Treatment Program each Monday through Friday for 9 weeks. Participants were randomly assigned possible drug condition orders of 0.15 mg/kg t.i.d., 0.3 mg/kg t.i.d. and 0.6 mg/kg t.i.d. and placebo<br>Average methylphenidate dosages: 5 mg, 10 mg and 18 mg for 0.15 mg/kg, 0.3 mg/kg and 0.6 mg/kg doses, respectively<br>Administration schedule: 7:45 AM, 11:45 AM and 3:45 PM<br>Duration of each medication condition: Each dose varied daily and was repeated 3 or 4 times within each behavioural treatment condition<br>Study duration: Monday through Friday for 9 weeks, totalling 45 days<br>Washout before study initiation: 1 week<br>Medication-free period between interventions: 0 to 2 days<br>Titration period: none<br>Treatment compliance: not stated<br>Cointervention: Three behavioural conditions (no behaviour modification, low-intensity behaviour modification and high-intensity behaviour modification) are delivered in random order, with each condition lasting 3 weeks. Parents attended training sessions and implemented behaviour programmes at home |
| Outcomes | **Non-serious adverse events**<br>1. Pittsburgh Side Effects Rating Scale: completed daily by camp staff and parents |
| Notes | Sample calculation: not stated<br>Ethics approval: yes; by the Health Sciences Institutional Review Board (IRB) of the University of Buffalo<br>**Comment from study authors**<br>1. Limitations: Trial duration of only 9 weeks, lack of daily completion of mood assessments and limited generalisation potential due to a population of predominantly Caucasian and middle-class participants<br>**Key conclusion of study authors**<br>1. Methylphenidate and behaviour modification therapy are tolerable and effective treatments for children with ADHD and severe mood dysregulation, but additional treatments may be needed to optimise their functioning<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking MPH before randomisation: yes; excluded patients with prior serious reactions to methylphenidate<br>Any withdrawals due to adverse events: 1 withdrew because of tic-like movements<br>Email correspondence with study authors: August 2014. Obtained supplemental information regarding randomisation, allocation concealment and handling of missing data. Not possible to retrieve safety data |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random orders were generated by computer with the restrictions that each condition occurred at least once in each week. Children were assigned to previously generated codes at enrolment |
| Allocation concealment (selection bias) | Low risk | Because this was a cross-over study in which all children received all conditions multiple times, each child's entire 9-week schedule was assigned at once. Treatment orders were concealed in an opaque envelope and were stored in a locked cabinet in the medication lab. Only authorised staff members had access to this cabinet |
| Blinding of participants and personnel (performance bias) | Low risk | Double-blind. Children, parents and staff were blinded to medication conditions. Placebo and methylphenidate were packaged in identical opaque capsules to maintain blinding |
| Blinding of outcome assessment (detection bias) | Low risk | Double-blind. Parents and staff were blinded to medication conditions |
| Incomplete outcome data (attrition bias) | Low risk | ITT<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Low risk | Outcomes reported according to protocol |
| Vested interest bias | High risk | This study was funded by National Institute of Mental Health (NIMH) Grant MH62946 and a Klingenstein Third Generation Foundation Fellowship in Child and Adolescent Depression Research<br>Conflicts of interest: Several authors have affiliations with pharmaceutical companies |

*Whalen 1990*

| Methods | Two cross-over trials with 3 interventions conducted 3 years apart<br>1. Methylphenidate 0.3 mg/kg<br>2. Methylphenidate 0.6 mg/kg (maximum 25 mg)<br>3. Placebo |
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| Participants | Number of participants screened: unknown<br>Number of participants included: study one 24, study two 25. Participants were randomly assigned to 1 of the possible drug condition orders<br>Number of participants followed up: study one 24 (22 boys, 2 girls), study two 25 (25 boys)<br>Number of withdrawals: study one 0, study two 0<br>ADHD diagnosis: study 1 DSM-III-R, study 2 DSM-III<br>Age: study one mean 9 years 8 months (range 6.4 to 13.2 years), study two mean 9 years 1 month (range 6.4 to 12.5 years)<br>IQ: no mental retardation (both studies)<br>Methylphenidate naive: 0 % (both studies)<br>Ethnicity: study one: Caucasian (92%), African American (4%), Hispanic (4%); study 2: Caucasian (72%), African American (12%), Asian (8%), Hispanic (8%)<br>Country: USA<br>Setting: out-patient clinic (Summer Treatment Program)<br>Comorbidity: study one not stated, study two no gross neurological dysfunction<br>Comedication: not stated<br>Sociodemographics: All were from middle- or low middle-income backgrounds (both studies)<br>**Inclusion criteria**<br>1. Study one<br>a. Primary diagnosis of ADDH<br>b. Taking methylphenidate on a regular basis before the programme<br>c. Conners' ADHD Stigma Questionnaire: ratings from parents > 15<br>2. Study two<br>a. Diagnosis of hyperactivity, ADD or ADDH<br>**Exclusion criteria**<br>1. No information |
| Interventions | Participants were randomly assigned to 1 of the possible drug condition orders of 0.3 mg/kg (study one) or 0.6 mg/kg (study two) of methylphenidate and placebo. As regards study two, a single dose of 25 mg was set as the upper limit<br>Mean methylphenidate dosage: 8.75 mg<br>Administration schedule: twice a day, morning and lunchtime<br>Duration of each medication condition: 1 week<br>Washout before study initiation: unknown<br>Medication-free period between interventions: 20 hours<br>Titration period: none<br>Treatment compliance: good (2 staff dispensed the medication for ingestion) |
| Outcomes | **General behaviour**<br>1. UC-Conners' Child Behavior Scale (UC-CCBS): rated once by staff and twice by naive university undergraduates |

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| **Notes** | Sample calculation: no<br>Ethics approval: no information<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; only participants taking maintenance dosage of methylphenidate or well titrated<br>**Comment from study authors**<br>1. Studies used similar procedures, with a few exceptions. The 2 sessions (i.e. study two) occurred between 1 and 2 weeks apart, rather than on consecutive days. Thus, the opportunity for medication washout was greater. Study two teams consisted of 3 rather than 4 players. In study two, 2 boys received scores below the hyperactivity cutoff on the maternal ratings, and paternal ratings yielded scores below the cutoff for 2 different boys<br>**Key conclusions of study authors**<br>1. In both studies, double-blind ratings done by naive and staff observers demonstrated nearly identical medication effects, that is, placebo-related increases in behaviour problems and methylphenidate-related increases in dysphoria<br>2. Ratings of medication effects proved remarkably resilient, showing an invulnerability to biasing influences introduced by general knowledge about research design, diagnostic status or treatment effects; or by specific knowledge about and experience with participating children<br>Email correspondence with study authors: January 2014. No supplemental information has been received |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | High risk | Study one: no information (unclear risk of bias)<br>Study two: Two thirds of the boys received medication first, and the remaining third received placebo first. (This unequal split resulted from the boys' simultaneous participation in a randomised 3-week dose-response assessment that was not pertinent to the present study) (high risk of bias) |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | High risk | Both active medication and placebo were placed in opaque gelatin capsules. Two staff, blinded to medication status, dispensed medication (low risk of bias)<br>Study 2: All staff were familiar with the boys, and some knew which boys had been diagnosed with ADHD, but none knew medication dosage or status (high risk of bias) |
| Blinding of outcome assessment (detection bias) | High risk | Study 2: All staff were familiar with the boys, and some knew which boys had been diagnosed with ADHD, but none knew medication dosage or status |
| Incomplete outcome data (attrition bias) | Low risk | No drop-outs<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Low risk | None |
| Vested interest bias | Unclear risk | No information |

## *Wigal 2003*

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| **Methods** | Double-blind, 2-stage, cross-over, pharmacokinetic and pharmacodynamic trial with 4 interventions<br>1. Ritalin 10 mg<br>2. Immediate-release or extended-release methylphenidate 40:60 (treatment C)<br>3. Immediate-release or extended-release methylphenidate 30:70 (treatment D)<br>4. Placebo<br>Phases: initial screening week, stage 1 cross-over of Ritalin vs placebo, stage 2 cross-over of treatment C and treatment D. Four weeks, with each study period lasting 1 week |

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| Participants | Number of participants screened: not stated<br>Number of participants included: 27. Participants were randomly assigned to 1 of 4 possible drug condition orders<br>Number of participants followed up: 25 (21 boys, 4 girls)<br>Number of withdrawals: 4<br>Diagnosis of ADHD: DSM-IV (subtype not stated)<br>Age: mean 10 ± 1.4 years (range 7 to 12)<br>IQ: not stated<br>Methylphenidate naive: not stated<br>Ethnicity: Caucasian (88%), African American (8%), Asian (4%), Hispanic (0%), other (0%)<br>Country: USA<br>Setting: out-patient clinic (laboratory and community)<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. One of 3 DSM-IV ADHD diagnostic criteria as specified in the Diagnostic Interview Schedule for Children or the Swanson, Nolan and Pelham, or both<br>2. 7 to 12 years of age<br>3. In need of methylphenidate treatment<br>4. Positive methylphenidate response<br>5. Prior successful treatment of ADHD symptoms with a methylphenidate product without adverse events<br>6. Methylphenidate products restricted to immediate-release methylphenidate twice daily, with the first daily dose required to be between 7.5 and 15 mg, and the second daily dose required to be between 5 and 15 mg, yielding a total daily dose of between 12.5 and 30 mg; or a sustained-release methylphenidate product taken once daily, with the single daily dose required to be 20 mg<br>7. Oral or written consent by both children and parents<br>8. Normal blood pressure, pulse rate and temperature<br>9. Girls had to be premenarchal<br>**Exclusion criteria**<br>1. Participation in another drug study during the preceding 30 days<br>2. Concurrent illness or condition with symptoms that could affect performance of any of the tests performed<br>3. Family history of drug abuse<br>4. Unable to follow instructions given in the study<br>5. Individuals who were severely depressed, psychotic, anxious, tense or agitated; or who had seizures or a family history of Tourette's syndrome, with primary diagnosis of oppositional defiant disorder or conduct disorder<br>6. Participants taking a medication in addition to methylphenidate for ADHD<br>7. Documented allergy or intolerance to methylphenidate<br>8. Individuals who were diagnosed with hyperthyroidism, were lactose-intolerant or had glaucoma<br>9. Participants unable to comply with blood drawing procedures during initial screening<br>10. Use of any of the following medications: amphetamines, pemoline, tricyclic antidepressants, MAO (monoamine oxidase) inhibitors, serotonin reuptake inhibitors, neuroleptics, benzodiazepines or benzodiazepine derivatives, clonidine, anticonvulsant medications, cough/cold preparations containing stimulants or sedatives |

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| Interventions | Participants were randomly assigned to 1 of 2 possible drug condition orders of methylphenidate and placebo in each of the 2 stages, 1 and 2, with each treatment period lasting 1 week<br><br>**Stage 1**<br><br>1. Treatment A<br>a. Participants were given 1 encapsulated tablet of Ritalin (10 mg) and 1 capsule of placebo after breakfast, and 1 encapsulated tablet of Ritalin (10 mg) after lunch for 7 days<br>2. Treatment B<br>a. Participants were given 2 placebo capsules after breakfast and 1 placebo capsule after lunch for 7 days<br><br>**Stage 2**<br><br>Half of the participants in each treatment group were randomly assigned to 20 mg/d dosage of methylphenidate, the other half to 40 mg/d dosage<br><br>1. Treatment C<br>a. Participants were given a daily morning dose (after breakfast) of two 20 mg capsules of the 40:60 prototype formulation or one 20 mg capsule of the 40:60 prototype formulation and 1 capsule of placebo; and a midday dose (after lunch) of 1 capsule of placebo for 7 days<br>2. Treatment D<br>a. Participants were given a daily morning dose (after breakfast) of two 20 mg capsules of the 30:70 prototype formulation or one 20 mg capsule of the 30:70 prototype formulation and 1 capsule of placebo; and a midday dose (after lunch) of 1 capsule of placebo for 7 days<br>b. Blood samples (3 mL) were collected pre-dose and at 0.5, 1.5, 2, 3, 4.5, 6, 7.5 and 9 hours after the morning dose on the last day (Saturday) of each treatment week<br><br>Mean methylphenidate dosage: 20 mg/d or 40 mg/d<br><br>Administration schedule: once daily or twice daily<br><br>Time points: mornings and after lunch<br><br>Duration of each medication condition: 1 week<br><br>Washout before study initiation: not stated<br><br>Medication-free period between interventions: 1 day (Sundays)<br><br>Titration period: none<br><br>Treatment compliance: not stated |

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| Outcomes | **ADHD symptoms**<br>1. Swanson, Kotkin, Agler, M-Flynn and Pelham (10-item) Scale: deportment and attention ratings performed every 1.5 hours (0 to 9 hours) at the end of each treatment week, by laboratory classroom teachers<br>2. Swanon, Kotkin, Agler, M-Flynn and Pelham (10-item) Scale: rated on weekdays by community classroom teachers<br>3. Conners, Loney and Milich (16-item): rated Monday, Wednesday and Friday by community classroom teachers and parents<br>**General behaviour**<br>1. Conners, Loney and Milich (16-item) Scale: ratings performed once every Monday, Wednesday and Friday of each treatment week by the regular community classroom teacher and the parents<br>**Non-serious adverse events**<br>1. Side Effects Rating form completed during all treatments by the children's regular community classroom teacher on Monday, Wednesday and Friday of each treatment week, daily by parents and each Saturday by the University of California at Irvine Child Developmental School (UCI-CDC) classroom teacher<br>2. All adverse events occurring during the study were reviewed by the investigator to assess their relationship to drug treatment (unrelated, unlikely, possibly, probably, almost certainly)<br>3. In addition, each sign or symptom reported was graded on a 3-point scale (mild, moderate or severe), and date and time of onset, time relationship to drug dosing, duration and outcome were noted<br>4. Clinical laboratory tests were performed at the local laboratory at baseline and at the end of the trial, and included blood count with differential, biochemistry (Na (sodium), K (potassium), Ca (calcium), PO4 (phosphate), total protein, glucose, alkaline phosphatase, AST (aspartate aminotransferase), ALT (alanine aminotransferase), total bilirubin, creatinine, albumin) and urinalysis (osmolality, pH (power of hydrogen) level, glucose, protein, white blood cells and casts)<br>5. Vital signs, including blood pressure and heart rate, were measured at each visit to the laboratory classroom<br>6. Body weight: 36.9 ± 7.6 kg<br>7. Height: 142 ± 8.4 cm |
| Notes | Sample calculation: not stated<br>Ethics approval: yes; study protocol and participant's informed consent form were approved by the Institutional Review Board (Office of the Vice Chancellor for Research, University of California at Irvine)<br>**Key conclusion of study authors**<br>1. Both methylphenidate formulations, given once in the morning, were superior to placebo and comparable with Ritalin b.i.d. treatment on all primary efficacy measures<br>**Comments from review authors**<br>1. Prototype formulation used - this may not be bioequivalent to the marketed formulation<br>2. Selective reporting of safety findings - omission of data obtained by adverse events rating form. Pre-specified primary outcome measure for efficacy (of prototype formulations versus placebo) - regular community classroom teacher. Conners' Global Index scores from Collegiate Learning Assessment (CLA) results presented only in Figure 4; no mean (SD) values provided in publication<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; methylphenidate tolerability was an inclusion criterion. Serious adverse events were an exclusion criterion<br>Email correspondence with study authors: July 2014. Emailed study authors twice for supplemental information but have received no response |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
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| Random sequence generation (selection bias) | Low risk | Qualified participants were randomly assigned to a 2-stage, double-blind study sequence consisting of 4 study treatments, each lasting for a period of 1 week |
| Allocation concealment (selection bias) | Low risk | Ritalin (10 mg) tablets were placed into capsule shells by Eurand Americas Incorporated. Resulting capsules were tested according to US Pharmacopeial Convention (USP) dissolution conditions for methylphenidate tablets and showed a dissolution profile comparable with intact Ritalin tablets. All medications were supplied in white, opaque, size 3, hard gelatin capsule shells, and were packaged in blister cards to enhance compliance |
| Blinding of participants and personnel (performance bias) | Low risk | Ritalin (10 mg) tablets were placed into capsule shells by Eurand Americas Incorporated. Resulting capsules were tested according to US Pharmacopeial Convention (USP) dissolution conditions for methylphenidate tablets and showed a dissolution profile comparable with intact Ritalin tablets. All medications were supplied in white, opaque, size 3, hard gelatin capsule shells, and were packaged in blister cards to enhance compliance |
| Blinding of outcome assessment (detection bias) | Unclear risk | No information |
| Incomplete outcome data (attrition bias) | High risk | Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): yes |
| Selective reporting (reporting bias) | Unclear risk | "Because the administration of the Side Effects Rating Form involved queries about specific adverse events, the frequency of adverse events reported in the parents' and teachers' Side Effect Rating Form was higher than that obtained from the reports elicited by general inquire (data not shown)" |
| Vested interest bias | High risk | Funding for this study was provided by Celltech Americas Incorporated<br>Conflicts of interest: Some study authors are working for Celltech Americas Incorporated |

*Wigal 2004*

| Methods | Four-week, randomised, double-blind, placebo-controlled, ITT, parallel trial conducted at 12 US centres with 3 arms<br>1. Dexmethylphenidate<br>2. Dex,l-methylphenidate<br>3. Placebo |
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| Participants | Number of participants screened: 174<br>Number of participants included: 132 (116 boys, 16 girls)<br>Number of participants randomly assigned: dexmethylphenidate 44, dex,l-methylphenidate 46, placebo 42<br>Number of participants followed up: dexmethylphenidate 42, dex,l-methylphenidate 40, placebo 37<br>Number of withdrawals: dexmethylphenidate 2, dex,l-methylphenidate 6, placebo 5<br>Diagnosis of ADHD: DSM-IV (combined (64%), hyperactive-impulsive (1%), inattentive (35%))<br>Age: mean 9.8 years (range 6 to 17)<br>IQ: not stated. No mental retardation<br>Methylphenidate naive: 95 (72%)<br>Ethnicity: Caucasian (78%), African American (14%), other (8%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: no<br>Comedication: no<br>Sociodemographics: not stated. No significant differences in baseline demographics were noted between the 2 groups<br>**Inclusion criteria**<br>1. Enrolled in elementary school<br>2. Within 30% of normal body weight<br>3. Anticipated as available for the entire length of the study<br>4. Female participants were required to be pre-menarche<br>**Exclusion criteria**<br>1. History or evidence of cardiovascular, renal, respiratory (other than asthma/allergy), endocrine or immune system disease<br>2. History of substance abuse<br>3. Hypersensitivity to dex,l-methylphenidate or other stimulants<br>4. Treatment with any investigational drug within 30 days of screening<br>5. Any other significant central nervous system disorders such as mental retardation, Tourette's or chronic tic disorder, psychosis, pervasive developmental disorder, eating disorders, obsessive-compulsive disorder, impulse control disorder or sleep disorders requiring medication, major depressive disorder or generalised anxiety disorder<br>6. Treatment with antidepressants (tricyclic antidepressants, serotonin reuptake inhibitors and monoamine oxidase inhibitors), sedative/hypnotics (e.g. barbiturates, benzodiazepine), neuroleptic/antipsychotics, mood stabilisers; anticonvulsants, beta-blockers, α2-agonists, thyroid medications and long-term oral steroids |
| Interventions | Participants were randomly assigned to immediate-release methylphenidate (dex- or d,l- racemats) or placebo<br>Mean methylphenidate dosage: dexmethylphenidate 18.25 mg/d, dex,i-methylphenidate 32.14 mg/d<br>Administration schedule: twice daily in the morning (7:00 AM to 8:00 AM) and at noon (11:30 AM to 2:30 PM)<br>Duration of intervention: 4 weeks<br>Titration period: maximum 3 weeks initiated after randomisation, included in the 4 weeks of intervention<br>Treatment compliance: not stated |

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| Outcomes | **ADHD symptoms**<br>1. Swanson, Nolan and Pelham ADHD Rating Scale - Teacher Version: teacher-rated, at baseline and twice weekly for 4 weeks, in the afternoon<br>2. Swanson, Nolan and Pelhan ADHD Rating scale - Parent Version: parent-rated, at baseline and daily on the weekend for 4 weeks, at 3:00 PM and 6:00 PM<br>**Non-serious adverse events**<br>1. Occurrence and severity, monitored by investigator, at weekly visits<br>2. Laboratory tests, physical examination findings and vital signs |
| Notes | Sample calculation: yes<br>Ethics approval: yes; approved by the institutional review board at each centre<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Comments from study authors**<br>1. Post hoc contrasts of small differences between dexmethylphenidate and dex,l-methylphenidate conditions were not statistically significant in this between-participant design<br>2. Three participants who did not meet the criteria set for a placebo response during the lead-in period were inadvertently entered into the double-blind phase (2 randomly assigned to dex,l-methylphenidate, 1 to placebo), which was a violation of the protocol<br>**Key conclusions of study authors**<br>1. For treatment of ADHD, an average titrated dose of 18.25 mg/d of dexmethylphenidate is as efficacious and safe as an average titrated dose of 32.14 mg/d of dex,l-methylphenidate<br>2. Both active treatments have large effect sizes. Thus, dexmethylphenidate and dex,l-methylphenidate appear to provide similar efficacy<br>**Comment from review authors**<br>1. We have not used these data, as reported data could not be used in our meta-analyses<br>Email correspondence with study authors: January 2014. Not possible to obtain data from study authors |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "Randomised" |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | Drug (dexmethylphenidate and dex,l-methylphenidate) and placebo were identical in appearance |
| Blinding of outcome assessment (detection bias) | Low risk | Double-blind |
| Incomplete outcome data (attrition bias) | Unclear risk | Sample size calculations were based on a clinically meaningful effect size of 0.75 in the change in score over 4 weeks on the teacher-rated Swanson, Nolan and Pelham Scale between dexmethylphenidate and placebo groups. Efficacy parameters were performed on the ITT sample, which included participants who received medication, had a baseline efficacy evaluation and had ≥ 1 post-baseline efficacy evaluation<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Low risk | No protocol published<br>All pre-specified outcomes of interest have been reported |
| Vested interest bias | High risk | This study was supported by Celgene Corporation<br>Conflicts of interest: Dr. Wigal reports extensive disclosure |

*Wigal 2013*

| Methods | Four- to six-week, open-label treatment (dose optimisation), cross-over, 2-week double-blind trial with 2 interventions<br>1. Methylphenidate (NWP06 - liquid formulation of extended-release methylphenidate)<br>2. Placebo<br>Phases: 2 |
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| Participants | Number of participants screened: 45 (32 boys, 12 girls)<br>Number of participants included: 44. Participants were randomly assigned to 1 of the possible drug condition orders<br>Number of participants followed up: 39<br>Number of withdrawals: 6<br>Diagnosis of ADHD: DSM-IV (combined (70.5%), hyperactive-impulsive (2.3%), inattentive (27.3%))<br>Age: mean 8.8 years (range 6 to 12)<br>IQ: not stated<br>Methylphenidate naive: 0 (0%)<br>Ethnicity: White 35 (79.5%), Black/African American 4 (9.1%), Asian 3 (6.8%), other 2 (4.5%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: elimination disorder (4; 9.1%), oppositional defiant disorder (8; 18.2%), specific phobias (2; 4.5%)<br>Comedication: no<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. ADHD diagnosis by psychiatrist, psychologist, developmental paediatrician or paediatrician<br>2. Pharmacological treatment for ADHD and has experienced suboptimal efficacy or a safety or tolerability issue with current regimen, or has been in need of a long-acting liquid formulation<br>3. Conners' Global Index Scale score > 3<br>4. ADHD Rating Scale score (Hyperactive-Impulsive or Inattentive subscale) > 90th percentile for age and sex<br>**Exclusion criteria**<br>1. Comorbidity (DSM-IV Axis I), with the exceptions of specific phobia, motor skills disorders, oppositional defiant disorder, sleep disorders, elimination disorders, adjustment disorders, learning disorders or communication disorders<br>2. IQ < 80<br>3. Chronic disease: seizure disorder, thyroid disease, Tourette's disorder or family history of Tourette's disorder or tics, serious cardiac conditions, cardiomyopathy, serious arrhythmias, structural cardiac disorders, glaucoma or severe hypertension<br>4. Any investigational medication 15 days before screening<br>5. Atomeoxetine (ATX) inhibitor 30 days before screening |
| Interventions | Participants were randomly assigned to different sequences of methylphenidate and placebo<br>Mean methylphenidate dosage: 32.8 mg/d<br>Administration schedule: q.i.d.<br>Duration of each medication condition: 1 week<br>Washout before study initiation: yes (1 day for stimulants)<br>Medication-free period between interventions: no<br>Titration period: 3 weeks before randomisation<br>Treatment compliance: 2 withdrawals of assent/consent, 2 adverse events, 1 lack of efficacy, 1 LTFU |

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| Outcomes | **ADHD symptoms**<br>1. Swanson, Kotkin, Agler, M-Flynn and Pelham Scale, ADHD Rating Scale (open-label phase)<br>**Non-serious adverse events**<br>42 participants (93.3%) experienced a treatment-emergent adverse event. Three (6.7%) participants experienced severe adverse effects (affect lability, aggression and initial insomnia), and 2 (4.4%) participants had to discontinue medication (affect lability and aggression)<br>1. Open-label phase: Participants experienced decreased appetite (55.6%), abdominal pain upper (42.2%), affect lability (26.7%), initial insomnia (22.2%), insomnia (17.8%) and headache (17.8%). Other adverse events reported in more than 5% of participants included vomiting, diarrhoea, logorrhoea, aggression, dizziness, irritability, fatigue, upper respiratory tract infection, cough and flushing<br>2. Double-blind phase: 11 (24.4%) participants had an adverse event while receiving NWP06, and 5 (11.1%) participants had an adverse event while receiving placebo |
| Notes | Sample calculation: no<br>Ethics approval: yes<br>**Comments from study authors**<br>1. "This study of NWP06 allowed inclusion of patients who were either treatment naive or had previously been treated with stimulants (...)"; "Subjects were required to have been in need of pharmacological treatment for ADHD (...)"<br>2. "Our population more closely reflects a real-world population and provides a more rigorous test of the study drug"<br>**Key conclusion of study authors**<br>1. NWP06 resulted in significant improvement in the Swanson, Kotkin, Agler, M-Flynn and Pelham-combined score at 4 hours post dose as compared with placebo among completers. This study shows that NWP06 significantly improved ADHD symptoms in school-aged children and was well tolerated<br>**Comments from review authors**<br>1. Laboratory school environment and lack of the ADHD Rating Scale<br>2. Race/ethnicity does not reflect a real-world population<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: not clear<br>Any withdrawals due to adverse events: yes (n = 2)<br>Email correspondence with study authors: emailed study authors to request additional information but have not received a response |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not stated |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | High risk | Results from open-label phase |
| Blinding of outcome assessment (detection bias) | High risk | Results from open-label phase |
| Incomplete outcome data (attrition bias) | High risk | Participants had to be in treatment with suboptimal efficacy (no inclusion of placebo responders)<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): Six participants were LTFU during the open-label titration phase, 2 as a result of adverse events. These participants are not included in our analyses |
| Selective reporting (reporting bias) | Low risk | ADHD Rating Scale not reported (used only in the open phase) |
| Vested interest bias | High risk | Study received funds from NextWave Pharmaceutics (Belden and Berry are with NextWave)<br>Conflicts of interest: All study authors are affiliated with NextWave Pharmaceuticals |

### *Wigal 2014*

| Methods | Cross-over trial with 2 interventions<br>1. Methylphenidate-MLR<br>2. Placebo<br>Phases: 4<br>1. Screening/washout period (< 4 weeks)<br>2. Open-label dose-optimisation period<br>3. Randomised, double-blind, placebo-controlled, cross-over design<br>4. 30-day safety follow-up period |
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| Participants | Number of participants screened: 32<br>Number of participants included: 26 (in open-label phase). Participants were randomly assigned to 1 of 2 possible drug condition orders<br>Number of participants followed up: 20<br>Number of withdrawals: 6<br>Diagnosis of ADHD: DSM-IV-TR (combined (n = 11), hyperactive-impulsive (n = 3), inattentive (n = 12))<br>Age: mean 8.7 years (range 6 to 12)<br>IQ: mean not stated (range 86 to 133)<br>Sex: 12 boys, 10 girls<br>Methylphenidate naive: none<br>Ethnicity: White (82%), Black (9%), Asian (5%), Hispanic or Latino (23%), other (5%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: 11; generalised anxiety disorder, enuresis, oppositional defiant disorder, chronic motor or vocal tic disorder, transient tic disorder<br>Comedication: no<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Children (male or female) 6 to 12 years of age<br>2. Any of the 3 subtypes of ADHD as defined by DSM-IV-TR, ADHD-RS-IV total or subscale score > 90th percentile relative to the general population of children by age and sex<br>3. Naive to treatment for ADHD or inadequately managed on current treatment regimen<br>4. Negative illicit drug and alcohol test results at screening and at each visit to the research site<br>**Exclusion criteria**<br>1. IQ > 80<br>2. Any severe psychiatric or significant comorbid condition<br>3. Use of a monoamine oxidase inhibitor or any psychotropic medication with central nervous system effects < 14 days of screening, or any experimental drug or medical device > 30 days of screening<br>4. Clinically significant electrocardiogram (ECG), or any laboratory abnormality<br>5. Any participant unable or unwilling to follow directions and complete study assessments or take oral capsules |
| Interventions | Participants were randomly assigned to 1 of 2 possible drug condition orders of methylphenidate (15 mg, 20 mg, 30 mg or 40 mg) and placebo<br>Mean methylphenidate dosage: 32 mg<br>Administration schedule: once a day<br>Time points: in the morning<br>Duration of each medication condition: 1 week<br>Washout before study initiation: 2 days<br>Medication-free period between interventions: not stated<br>Titration period: yes; 2 to 4 weeks before randomisation<br>Treatment compliance: yes; verified at scheduled study visits by study personnel who examined documentation of drug dispensed, drug consumed and remaining drug, and recorded the information on the drug reconciliation form<br>Compliance was calculated to be > 82% throughout the study |

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| Outcomes | **ADHD symptoms**<br>1. Swanson, Kotkin, Agler, M-Flynn and Pelham: total scores, trained observers, post dose over time points 1.0, 2.0, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5 and 12.0 hours<br>2. Swanson, Kotkin, Agler, M-Flynn, and Pelham: attention and deportment scores averaged over all post-dose time points<br>3. ADHD Rating Scale, Fourth Edition: clinician-rated, 3.0 hours post dose each laboratory day<br>**Non-serious adverse events**<br>1. Safety and tolerability assessments |
| Notes | Sample calculation: yes<br>Ethics approval: yes<br>**Comment from study authors**<br>1. Limitations of this study: Study was slightly underpowered and produced a study population that may not be reflective of the general population of children and adolescents with ADHD<br>**Key conclusions of study authors**<br>1. In this study, methylphenidate-MLR administered to children 6 to 12 years of age demonstrated a significant decrease in scores on the Swanson, Kotkit, Agler, M-Flynn and Pelham Scale compared with placebo<br>2. Onset of action in this population is 1 hour, and duration of efficacy is sustained to 12 hours post dose<br>3. Future studies that include measurement of efficacy earlier than hour 1.0 and extend beyond hour 12.0 would add clarity to the precise onset and duration of clinical efficacy<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; 2 withdrew during the open-label phase as the result of lack of efficacy<br>Any withdrawals due to adverse events: yes (n = 1)<br>Email correspondence with study authors: April 2015. Obtained supplemental information from study authors |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | High risk | Randomisation was determined by using a table of random numbers. Randomisation tables were provided to the randomisation monitor, who created unblinding envelopes and packaged the drug with blinded labels |
| Allocation concealment (selection bias) | High risk | One participant received placebo at 2 periods - the method was not efficacious |
| Blinding of participants and personnel (performance bias) | Low risk | All sponsor representatives, investigators, participants and independent raters remained blinded until after data were locked |
| Blinding of outcome assessment (detection bias) | Low risk | Yes; this has been done |
| Incomplete outcome data (attrition bias) | Low risk | ITT were used<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo-responders): no; no exclusion of methylphenidate non-responders after randomisation |
| Selective reporting (reporting bias) | Low risk | No selective reporting bias |
| Vested interest bias | High risk | Study was funded by Rhodes Pharmaceuticals L.P.<br>Conflicts of interest: Several study authors work for, or have received grant and research support or both from pharmaceutical companies |

*Wilens 2006b*

| Methods | Two-week, randomised, double-blind, 15-centre, parallel trial with 2 arms<br>1. OROS methylphenidate<br>2. Placebo<br>Phases: preceded by a 4-week, open-label, dose-titration phase, and followed by an 8-week, open-label, follow-up phase |
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| Participants | Number of participants screened: not stated<br>Number of participants included: 220 in the 4-week dose-titration phase<br>Number of participants randomly assigned: 177 (142 boys, 35 girls); methylphenidate 87, placebo 90<br>Number of withdrawals: methylphenidate 16, placebo 28<br>Number of participants followed up: 171; number completing follow-up: 135<br>Diagnosis of ADHD: DSM-IV (subtype not stated)<br>Age: mean 14.6 years (range 13 to 18)<br>IQ: not stated<br>Methylphenidate naive: not stated<br>ADHD treatment-naive: 24<br>Ethnicity: Caucasian (75.1%), African American (13.6%), other (11.3%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated. The 2 groups were similar demographically, but the placebo group had a greater ratio of males (P value < 0.04)<br>**Inclusion criteria**<br>1. Diagnosis of attention deficit hyperactivity disorder (ADHD), as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV)<br>2. Children's Global Assessment Scale rating of 41 to 70 at baseline (screening phase)<br>3. Between 8 and 13 years of age<br>**Exclusion criteria**<br>1. Participants who are known to not respond to methylphenidate<br>2. Adverse experiences from methylphenidate or hypersensitivity to Concerta or its components<br>3. Marked anxiety, tension or agitation<br>4. Psychiatric comorbidity requiring additional or different medication<br>5. Glaucoma, ongoing seizure disorder, psychotic disorder, Tourette's disorder or family history of Tourette's disorder, bipolar disorder, an eating disorder<br>6. Treatment with theophylline, coumarin, anticonvulsants<br>7. Severe gastrointestinal narrowing<br>8. Systolic or diastolic blood pressure at the 95th percentile or greater for age, sex and height at screening |
| Interventions | Participants were randomly assigned to OROS methylphenidate or placebo<br>Mean methylphenidate dosage: 0.84 mg/kg<br>Administration schedule: once daily<br>Duration of intervention: 2 weeks<br>Titration period: 4 weeks initiated before randomisation. All participants initiated therapy at 18 mg/d, and clinical response was measured after 1 week. If response to treatment was inadequate, as per the a priori study definition, the dose was titrated upward (in 18-mg increments) at 1-week intervals for up to 4 weeks, with maximum dose of 72 mg/d<br>Treatment compliance: not stated; 8-week, open-label follow-up on individualised dosage |

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| Outcomes | **ADHD symptoms**<br>1. ADHD Rating Scale, clinician- and parent-rated: completed at baseline and weekly during double-blind phase<br>**Serious adverse events**<br>1. Reported in only 1 participant during the open-label dose-titration phase of the study. While being treated with OROS methylphenidate 18 mg/d, a 16-year-old female participant with a history of depression and suicidal ideation threatened suicide on the third day of medication use after an argument with her mother. Decision was made to discontinue study medication, and symptoms resolved<br>2. No serious adverse events were reported during the double-blind phase<br>**Non-serious adverse events**<br>1. Heart rate and blood pressure, recorded by a clinician weekly throughout the whole study<br>2. ECG at screening and at end of double-blind phase of the study<br>3. Spontaneous reports to the investigator of adverse events recorded at weekly visits<br>4. Safety assessments made at monthly visit and every 2 weeks between monthly visits during follow-up<br>5. Height and weight assessed at baseline and at weeks 4 and 8 in the follow-up study<br>No participants experienced clinically important effects on ECG indexes, heart rate or blood pressure during the study |
| Notes | Sample calculation: yes<br>Ethics approval: yes; study was approved by the institutional review boards for all participating centres before the start of the study<br>Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; criteria of response, defined as ≥ 30% improvement from baseline on the investigator-scored ADHD Rating Scale. Participants who successfully completed the open-label dose-titration phase were assigned a randomisation number<br>**Comments from study authors**<br>1. Exclusion criteria were significant and possibly limited the generalisability of results<br>2. Participants may have had improved ADHD symptoms or psychosocial carry-over effects as a consequence of participation in the study, medication titration and regular meeting with study personnel<br>3. Our study was conducted partially during the summer, and this may have resulted in less stress on adolescents and overall improvement in both study groups. More sensitive measures of attention may be needed for adolescents with ADHD than for children<br>4. Participants were titrated to their individualised dosage before the double-blind phase of the study. This may have biased the results toward a positive response in the double-blind phase<br>The short duration of the double-blind phase may have decreased the likelihood of detecting potential rare adverse events. Rates of adverse events reported for OROS methylphenidate have been underestimated because participants entering this study phase were already stabilised on an affective tolerated dosage of medication<br>**Key conclusions of study authors**<br>1. In adolescents, once-daily OROS methylphenidate significantly reduced ADHD symptoms and was well tolerated at dosages up to 72 mg/d<br>2. Adolescents required, on average, a higher absolute dose but a lower weight-adjusted dose (mg/kg) of OROS methylphenidate than was previously reported in children<br>3. The incidence of adverse events was not related to dose<br>Email correspondence with study authors: December 2013 and Janurary 2014. Not able to make contact with study authors |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomised, but method was not described |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Low risk | Investigators were supplied with packages containing medication for each participant, as identified by randomisation number. Therefore, investigators and participants were blinded to whether a participant was receiving active medication or placebo |
| Blinding of outcome assessment (detection bias) | Low risk | Investigators were supplied with packages containing medication for each participant, as identified by randomisation number. Therefore, investigators and participants were blinded to whether a participant was receiving active medication or placebo |
| Incomplete outcome data (attrition bias) | High risk | Non-responders not included. LOCF technique was used for all assessments in the double-blind phase. Of 182 (83%) participants who successfully achieved the criteria for improvement at the dose-titration phase, only 177 were randomly assigned to the double-blind phase, because 5 reached the criteria after the double-blind phase was closed. Of 177 randomly assigned participants, 1 did not enter the double-blind phase, and efficacy data were not collected for another participant. Therefore, 175 participants were included in the efficacy analysis of the double-blind phase, but 177 were included in the dosage and safety analysis |
| Selective reporting (reporting bias) | Low risk | No major violation compared with what is reported in ClinicalTrials.gov<br>All pre-specified outcomes of interest have been reported |
| Vested interest bias | High risk | Funded by McNeil Consumer and Specialty Pharmaceuticals<br>Conflicts of interest: Several study authors have had commitments (e.g. speakers, consultants, advisors) with various pharmaceutical companies |

*Wilens 2008*

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| Methods | Open-label, 5-week, dose-optimisation period. This dose was maintained during the subsequent 3 weeks of the trial, except for 1 day per week of 3-way cross-over assessment<br>Randomised, double-blind, 8-centre, 3-way, 3-week, cross-over trial with 2 interventions<br>1. Methylphenidate<br>2. Placebo |

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| Participants | Number of participants screened: 148<br>Number of participants included: 128 in open-label, dose-titration; 120 randomly assigned to 1 of 3 possible drug orders<br>Number followed up: 127 for safety and 117 for efficacy<br>Number of withdrawals: 2<br>**Characteristics of the 127 followed up for safety**<br>Sex: 84 boys, 42 girls<br>Diagnosis of ADHD: DSM-IV (combined or hyperactive-impulsive (92.1%) inattentive (not stated))<br>Age: mean 8.8 years (SD 1.84; range 6 to 12)<br>IQ: > 80<br>Methylphenidate naive: not stated<br>Ethnicity: Caucasian (63.2%), African American (15.4%), Asian (not stated)<br>Country: USA<br>Comorbidity: not allowed<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Characteristics of the 117 followed up for efficacy**<br>Sex: 75 boys, 42 girls<br>Diagnosis of ADHD: DSM-IV (type not stated)<br>Age: mean 8.8 years (range 6 to 12)<br>IQ: > 80<br>MPH-naive: not stated<br>Ethnicity: Caucasian (63.2%), African American (15.4%), Asian (0%), other (21.4%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: not allowed<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Diagnosed with ADHD according to DSM-IV-T<br>2. Minimum IQ score of 80<br>**Exclusion criteria**<br>1. Conduct disorder or comorbid illnesses that contraindicated or could confound methylphenidate transdermal system treatment<br>2. History of failing to respond to psychostimulant treatment<br>3. Taken another investigational product within 30 days of screening or participated in other research trials involving drug treatment during the course of the study<br>4. Safety population consisted of 127 participants, who received ≥ 1 dose of study medication<br>11 participants discontinued before the double-blind randomisation phase, resulting in an ITT population of 117 participants<br>Seven participants discontinued before the double-blind randomisation phase, 3 were randomly assigned but did not undergo methylphenidate transdermal system (MTS) treatment<br>Two participants did not complete the analogue classroom phase of the study: 1 because of an application site reaction, and 1 because of an adverse event (conjunctivitis), resulting in a total of 115 study completers |

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| Interventions | Participants were randomly assigned to 1 of 3 possible drug orders of methylphenidate (4 and 6 hours) and placebo<br><br>Mean methylphenidate dosage: 10 mg patch (n = 15), 15 mg patch (n = 34), 20 mg patch (n = 32) and 30 mg patch (n = 36)<br><br>Administration schedule: once daily in the morning; patch worn for 9 hours daily, and for 4 or 6 hours for cross-over assessments<br><br>Duration of each medication condition: 1 day<br><br>Washout before study initiation: none; in-between treatment with optimal dose of methylphenidate<br><br>Titration period: 5 weeks before randomisation<br><br>Treatment compliance: not stated |
| Outcomes | **ADHD symptoms**<br><br>1. Swanson, Kotkit, Agler, M-Flynn and Pelham: teacher-rated at randomisation (week 5) and 2 hours after patch application at end of treatment (week 6, 7, 8)<br><br>**Quality of life**<br><br>1. ADHD Impact Module-Child - Child Impact Scale and Family Impact Scale: rated at baseline, at randomisation (week 5) and at end of study (week 8)<br><br>**Non-serious adverse events**<br><br>1. Vital signs were evaluated at screening, at baseline and at weeks 1 to 8<br>2. Erythema, edema, papules and vesicles, discomfort, haematology, urinalysis and electrocardiographic measures were completed at screening, at baseline and at weeks 5 and 8<br><br>No clinically meaningful changes from baseline were observed in vital signs, ECG, urinalysis and haematological results or physical examinations. Adverse events were recorded from the time informed consent was signed until 30 days (week 12) after the last drug treatment |

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| Notes | Sample calculation: yes; assuming a mean difference in Swanson, Kotkit, Agler, M-Flynn and Pelham deportment score of 2.0 between active treatment and placebo, an SD of 5.0, a between correlation of 0.2, 90% power and a probability level of .05 (2-sided), it was estimated that approximately 102 participants were needed to complete the double-blind, cross-over phase of the study<br><br>Ethics approval: yes; institutional review board at each site approved the study<br><br>**Comments from study authors**<br><br>1. Important to note that participants who failed to respond to psychostimulants in the past and those with conduct disorder were excluded from the study. Therefore, results of this study should not be extrapolated to these patient populations<br>2. From Manos in Wilens 2008: Lack of placebo comparison has the potential to confound the findings of this study. The relatively short study duration (about 2 months) may not be sufficient to capture some emerging changes in health-related quality of life<br><br>**Key conclusion of study authors**<br><br>1. All efficacy measures indicated that 4- and 6-hour wear times improved ADHD symptoms<br><br>**Comments from review authors**<br><br>1. Treatment period is 1 day, 1 week apart for the 3 phases, and all participants are treated with methylphenidate at optimal titrated dose in-between<br>2. Quality of life assessments are aggregated for all (not possible to assess methylphenidate vs placebo)<br><br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; participants with a history of failing to respond to psychostimulant treatment were also excluded<br><br>Any withdrawals due to adverse events: yes; 1 (conjunctivitis)<br><br>Email correspondence with study authors in April to June 2014. Emailed study authors twice to ask for additional data but never received a response |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Single randomisation schedule prepared by an independent statistician using computer software that generated random numbers |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | Each participant wore 2 patches prepared by an unblinded pharmacist to maintain treatment blind |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not stated |
| Incomplete outcome data (attrition bias) | High risk | ITT population (more than 1 application of a study drug and pre-dose efficacy assessment at week 6). Participants who did not reach an optimal dose by week 5 were discontinued from the study<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders): yes; participants who did not reach an optimal dose by week 5 were discontinued from the study |
| Selective reporting (reporting bias) | Unclear risk | Protocol published. All pre-specified outcomes of interest have been reported |
| Vested interest bias | High risk | This study was funded by Shire Development Incorporated<br>Conflicts of interest: Several study authors have affiliations with medical companies |

*Wilens 2010*

| Methods | Blind, randomised, 4-week, cross-over trial with 2 interventions<br>1. Methylphenidate<br>2. Placebo |
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| Participants | Number of participants screened: unknown<br>Number of participants included: 36. Participants were randomly assigned to 1 of 2 possible drug condition orders<br>Number of participants followed up: 30 (25 boys, 5 girls)<br>Number of withdrawals: 4<br>Diagnosis of ADHD: DSM-IV (combined (53%), hyperactive-impulsive (3%), inattentive (43%))<br>Age: mean 9.17 years (SD 1.84; range 6 to 12)<br>IQ: > 70<br>Methylphenidate naive: 14 (47%)<br>Ethnicity: Caucasian (90%), African American (not stated), Asian (3%), Hispanic (not stated), other (7%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: oppositional disorder (70%), conduct disorder (7%), major depressive disorder (3%)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Male and female out-patients<br>2. 6 to 12 years of age<br>3. Diagnosis of ADHD by DSM-IV, as manifested in clinical evaluation and confirmed by structured interview<br>4. Participation in structured morning routine (e.g. school, camp, other organized activities)<br>**Exclusion criteria**<br>1. Mental retardation (IQ < 75)<br>2. Participants with a medical condition, or treatment that will jeopardise participant safety or affect the scientific merit of the study<br>3. Participants with moderate to severe dermatological atopy<br>4. Participants with known structural cardiac abnormalities<br>5. Organic brain disorders<br>6. Seizure disorder<br>7. Participants with Tourette's syndrome or a history of psychosis or bipolar disorder<br>8. Participants with current comorbid psychopathology that, in the investigator's opinion, will warrant immediate treatment or will interfere with safe execution of the protocol (i.e. anxiety or major depressive disorder rated as moderate on Conners' Global Index)<br>9. Participants with a history of intolerable adverse effects or non-response to methylphenidate<br>10. Pregnant or nursing females |
| Interventions | Participants were randomly assigned to 1 of 2 possible drug condition orders of methylphenidate (20 mg) and placebo<br>Mean methylphenidate dosage: not stated<br>Administration schedule: patch applied in morning and worn for 9 hours<br>Duration of each medication condition: 2 weeks<br>Washout before study initiation: none<br>Titration period: 1 week after randomisation<br>Treatment compliance: > 80% for all participants |

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| Outcomes | **ADHD symptoms**<br>1. ADHD Rating Scale: clinician-rated at baseline and weekly for 4 weeks<br>2. Conners' Global Index: parent-rated at baseline and weekly for 4 weeks (no data)<br>**Non-serious adverse events**<br>1. Adverse events and vital signs: clinician-rated at baseline and weekly for 4 weeks<br>2. ECG: clinician-rated at baseline and at end of study |
| Notes | Sample calculation: no<br>Ethics approval: not stated<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; participants with a history of no response or intolerability to methylphenidate were excluded for ethical reasons<br>**Comment from study authors**<br>1. Doses used are lower than US FDA-approved dose of 30 mg. It is unclear whether results of this study represent optimal response<br>**Key conclusion of study authors**<br>1. Early administration of methylphenidate transdermal system was associated with improved ADHD symptoms and before-school functioning in children with ADHD<br>Email correspondence with study authors: March/April 2014. We contacted the first study author twice to ask for supplemental data but have not received a response |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomly assigned |
| Allocation concealment (selection bias) | Low risk | Prescriptions filled by hospital pharmacy |
| Blinding of participants and personnel (performance bias) | Unclear risk | No additional information from study author |
| Blinding of outcome assessment (detection bias) | Unclear risk | Double-blind (participant, caregiver, investigator) |
| Incomplete outcome data (attrition bias) | High risk | ITT: participants who completed 1 week of treatment; LOCF<br>Selection bias: yes. Excluded participants not following 1 week of treatment |
| Selective reporting (reporting bias) | Low risk | Protocol published. All pre-specified outcomes of interest have been reported |
| Vested interest bias | High risk | This study and medication/placebo were funded by a grant through Shire Pharmaceuticals. Shire had no role in design, collection, analysis, interpretation, writing or decision to submit<br>Conflicts of interest: Some study authors have received research support from medical companies |

***Wilkison 1995***

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| Methods | Double-blind, placebo-controlled, cross-over trial with 2 interventions<br>1. Methylphenidate<br>2. Placebo<br>Phases: 2 |

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| Participants | Number of participants screened: not stated<br>Number of participants included: 16. Participants were randomly assigned to 1 possible drug condition order<br>Number of participants followed up: 16 implied (16 boys, 0 girls)<br>Number of withdrawals: not stated<br>Diagnosis of ADHD: DSM-III-R (subtype not stated)<br>Age: mean 10.2 years (range 8 to 13)<br>IQ: mean 112.6<br>Methylphenidate naive: 0%<br>Ethnicity: not stated<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: no<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Boys<br>2. 8 to 13 years of age<br>3. ADHD<br>4. Recruited from an out-patient clinic at a large metropolitan children's hospital in the USA<br>5. Conners' Hyperactivity Index score 1.5 SD above the norm on parent ratings<br>6. ≥ 6 months of treatment with methylphenidate<br>7. Confirmed DSM-III-R diagnosis<br>8. History of > 6 months of methylphenidate treatment<br>**Exclusion criteria**<br>1. No physical or psychiatric diagnosis other than ADHD<br>2. Evidence of learning disability<br>3. "Each parent and prescribing physician reported that the subject responded positively to MPH" |
| Interventions | Participants were randomly assigned to 1 of 2 possible drug condition orders of methylphenidate (normal dose) and placebo<br>Mean methylphenidate dosage: 0.030 mg/kg (range 0.08 to 1.10 mg/kg/d)<br>Administration schedule: not stated<br>Duration of each medication condition: 36 hours<br>Washout before study initiation: not stated<br>Titration period: not stated<br>Treatment compliance: not stated |
| Outcomes | **General behaviour**<br>1. Behaviour problems - Child Behavior Checklist, parent ratings. Data not reported |

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| **Notes** | Sample calculation: not described<br>Ethics approval: not described<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>**Key conclusion of study authors**<br>1. Stimulant effects on child's motivation to perform a task may compensate for deficits in other areas<br>**Comment from review authors**<br>1. All participants had been treated previously with methylphenidate for longer than 6 months; each parent and physician reported good response<br>Email correspondence with study authors: May 2014. We obtained supplemental information from study authors |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | From correspondence: generated by pharmacist (Magnusson 2014c [pers comm]) |
| Allocation concealment (selection bias) | Low risk | From correspondence: Recruiter had no involvement in and was blinded to allocation sequence (Magnusson 2014c [pers comm]) |
| Blinding of participants and personnel (performance bias) | Low risk | From correspondence: Pharmacist instructed parents (via instructions on pill bottle) regarding which pills should be administered and at what time ( Magnusson 2014c [pers comm]) |
| Blinding of outcome assessment (detection bias) | Low risk | See above |
| Incomplete outcome data (attrition bias) | Low risk | From correspondence: Approximately 2% of skin conductance and heart rate data were affected by participant movement and were replaced with interpolated values Physiological data were lost for 2 participants with ADHD and for 2 participants without ADHD. For 3 of the remaining 28 participants, 1 of the 4 repeated measurements of interbeat intervals was replaced with the mean of the participant's diagnostic group because his ECG recordings were inadequate (Magnusson 2014c [pers comm])<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Low risk | No reporting bias |
| Vested interest bias | Low risk | Research was supported by University of Utah Biomedical Sciences Research Grant and a grant from the University Research Committee<br>Conflicts of interest: no corporate affiliations described |

### *Wodrich 1998*

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| **Methods** | Three-week cross-over trial with 3 interventions<br>1. Methylphenidate 5 mg, twice daily<br>2. Methlphenidate 15 mg, twice daily<br>3. Placebo<br>**Phases**<br>1. Each drug condition lasted 7 days (Thursday through Wednesday)<br>2. "No washout period was deemed necessary, given the brief half-life and absence of carry-over effects of MPH [methylphenidate]" |

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| Participants | Number of participants screened: 123 ("treated in the clinic")<br>Number of participants included: 57 (47 boys, 10 girls)<br>Number of participants followed up: 57<br>Number of withdrawals: 66. Away on summer vacation (n = 30), teacher failed to complete all rating forms (n = 29), teacher marked 2 values indicated on a single dimension (n = 3), adverse medication side effect (n = 2), dropped out before child's medication trial was completed (n = 2)<br>Diagnosis of ADHD: DSM-III-R<br>Age: mean 8.5 years (SD 2.1; range 6 to 14)<br>IQ: not stated<br>Methylphenidate naive: not stated<br>Ethnicity: Caucasian "Anglo" 54 (95%), Hispanic 3 (5%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. DSM-III-R Diagnosis of ADHD, confirmed by a clinical psychologist<br>**Exclusion criteria**<br>1. No primary disorder "better explained the child's presenting symptoms" (e.g. mood disorder, anxiety disorder, adjustment disorder, pervasive developmental disorder) |
| Interventions | Participants were randomly assigned to 1 of 2 possible drug condition orders (5 mg methylphenidate or 15 mg methylphenidate) and placebo, given at 8:00 AM and 12:00 PM<br>Mean methylphenidate dosage: 10 mg/d, 30 mg/d and placebo<br>Administration schedule: 3-week, triple-blind, cross-over medication trial consisting of placebo, 5 mg of methylphenidate and 15 mg of methylphenidate, twice a day. Each drug condition lasted 7 days (Thursday through Wednesday)<br>Duration of each medication condition: 3 weeks<br>Washout before study initiation: approximately 20 hours (lunchtime until "immediately before school" the next day)<br>Titration period: not stated<br>Treatment compliance: not stated<br>Number of withdrawals: 2. Parents dropped out of the study before their child's medication trial was completed |
| Outcomes | **ADHD symptoms**<br>1. Abbreviated Conners' Rating Form<br>2. School Situations Questionnaire: "As our research concern was to locate tools helpful to school psychologists, we chose to address only the utility of using SSQ. For statistical analysis, scores from zero (no problem) to 9 (severe problem) were entered for each situation" (p 84)<br>**General behaviour**<br>1. Personality Inventory for Children<br>**Serious adverse events**<br>1. Side Effects Questionnaire<br>**Non-serious adverse events**<br>1. Side Effects Questionnaire |

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| **Notes** | Sample calculation: not stated<br>Ethics approval: not stated<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes<br>**Key conclusions of study authors**<br>1. School Situation Questionnaire ratings improved with methylphenidate treatment in all situations related to task performance (i.e. arriving at school; during individual seatwork, small group activities and lectures) but less so in non-task or unstructured situations<br>2. Many change scores were large enough to be clinically meaningful<br>3. Use of School Situations Questionnaire by school psychologists was discussed as a means of efficiently providing contextual information not available from ADHD dimensional rating scales<br>Email correspondence with study authors: June 2014. We obtained supplemental information from study authors. We contacted study author to ask for missing data, but s/he was not able to supply the data |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "Subjects then underwent a three-week, triple-blinded, cross-over medication trial consisting of placebo, 5 mg, and 15 mg of MPH dose twice a day (immediately before school and at lunchtime)" (p 83); "Order of administration was counterbalanced so that equivalent numbers of children received each sequence" (p 83) |
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | Low risk | "Subjects then underwent a three-week, triple-blinded, cross-over medication trial consisting of placebo, 5 mg, and 15 mg of MPH dose twice a day (immediately before school and at lunchtime). Each drug condition lasted seven days (Thursday through Wednesday)" (p 83); "Doses were prepared and packaged for the three week trial by a licensed pharmacist who split MPH tablets and placed them with lactose into re-sealable capsules. The placebo dose consisted of lactose-filled capsules only. Equivalent numbers of capsules (three) were dispensed at each dosing time to maintain uniformity and disguise presence/amount of<br>medication, as three capsules were required to encompass the largest dose (15 mg)" (p 83) |
| Blinding of outcome assessment (detection bias) | High risk | "This procedure was followed for three weeks, with the medication code being broken the final week and determination about medication efficacy and decision to continue addressed at that time" (p 84) |
| Incomplete outcome data (attrition bias) | Unclear risk | No information |
| Selective reporting (reporting bias) | Unclear risk | No information |
| Vested interest bias | Unclear risk | No information |

*Wolraich 2001*

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| **Methods** | Twenty-eight-day, randomised, parallel, double-blind clinical trial with 3 arms<br>1. OROS methylphenidate<br>2. Immediate-release methylphenidate<br>3. Placebo |

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| Participants | Number of participants screened: 405<br>Number of participants included: 312; OROS methylphenidate 94, immediate-release methylphenidate 94, placebo 89<br>Number of participants followed up: OROS methylphenidate 79, immediate-release methylphenidate 81, placebo 46<br>Number of withdrawals: OROS methylphenidate 15, immediate-release methylphenidate 13, placebo 43<br>Diagnosis of ADHD: DSM-IV (combined (73.4%), hyperactive-impulsive (7.1%), inattentive (19.5%))<br>Age: mean 9.0 years (range 6 to 12)<br>IQ: > 70<br>Sex: 233 boys, 49 girls<br>Methylphenidate naive: 20.2%<br>Ethnicity: Caucasian (84.4%), African American (7.4%), Asian (0.4%), Hispanic (3.5%), other (4.3%)<br>Country: USA<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder (41.8%), conduct disorder (11.3%), tic disorder (5.3%), anxiety disorder (1.4%), depression (0.7%)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. 6 to 12 years of age<br>2. Clinical diagnosis of any subtype of ADHD - had to be confirmed by the Diagnostic Interview Schedule for Children (Version 4), administrated by a trained interviewer<br>3. Patients who were taking methylphenidate or had taken it in the past had to have been on a total daily dose of methylphenidate (immediate-release or a combination of immediate-release/extended-release) of ≥ 10 mg but ≤ 60 mg<br>4. Patients had to agree to take the supplied study drug as the only medication for ADHD during the 4-week study period<br>5. IQ > 70<br>**Exclusion criteria**<br>1. Acute or serious chronic disease<br>2. Hypersensitivity to methylphenidate<br>3. Significant adverse experiences from methylphenidate<br>4. Taking a medication that would interfere with safe administration of methylphenidate<br>5. Glaucoma, Tourette's syndrome, ongoing seizure disorder or psychotic disorder<br>6. Girls who had reached menarche<br>During the course of the study, participants were allowed to receive behavioural interventions as long as the interventions had been initiated before the start of the study and did not change during the study. New behavioural therapy was not allowed during the course of the study |
| Interventions | Average total daily dose: immediate-release methylphenidate 29.5 mg per day (0.90.4 mg/kg/d), OROS methylphenidate 34.3 mg per day (1.1 to 0.5 mg/kg/d)<br>Administration schedule: 3 times a day<br>Duration of intervention: 4 weeks<br>Titration period: 4-week titration period before randomisation (open-label) for study participants who had not received methylphenidate for ADHD from their own practitioner in the 4 weeks before study entry. Participants who had taken methylphenidate during the 4 weeks before study entry were assigned to a dose level based on their pre-study therapeutic dose and regimen<br>Treatment compliance: not stated |

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| Outcomes | **ADHD symptoms**<br>1. IOWA Conners' Rating Scale: teacher- and parent-rated on day 27<br>2. Swanson, Nolan and Pelham Scale, Fourth Edition: teacher- and parent-rated, week 4<br>**Quality of life**<br>1. Child Global Assessment Scale |
| Notes | Sample size calculation: yes<br>Ethics approval: yes<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: yes; 111 who had not received methylphenidate before the study initially were enrolled into a dose-titration study. One of these did not enrol in the randomised study because the 54-mg dose was found to be ineffective<br>**Key conclusion of study authors**<br>1. Results of this study show that OROS methylphenidate administered once a day and immediate-release methylphenidate administered 3 times a day were significantly better than placebo and were not significantly different from each other for the primary efficacy measure, teacher IOWA Conners' Rating Scale, Inattention-Impulsivity-Overactivity subscale score, which evaluated attention and behaviour at school. Furthermore, significant improvement in attention and behaviour was seen in the first week for participants who were taking OROS methylphenidate qd or immediate-release methylphenidate t.i.d. compared with placebo, and this improvement was maintained throughout the 4 weeks of the study. These results were consistent across settings (home and school), raters (parents, teachers, clinical investigators) and measures (IOWA Conners' Rating Scale; Swanson, Nolan and Pelham, Fourth Edition; Peer Interaction; Global Assessments; Parent Satisfaction) and were statistically significant<br>Comments from review authors in July 2013: *c*orresponded with first study author, Wolraich, who answered all of our questions (Krogh 2013c [pers comm]) |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Within each dose level, participants were randomly assigned equally to OROS methylphenidate qd, immediate-release methylphenidate (overencapsulated Ritalin) t.i.d. or placebo in a 3-group parallel design. Stratified randomisation was conducted centrally at ALZA Corporation |
| Allocation concealment (selection bias) | Low risk | Double-dummy |
| Blinding of participants and personnel (performance bias) | Low risk | Double-blind; double-dummy |
| Blinding of outcome assessment (detection bias) | Low risk | Double-blind; double-dummy |
| Incomplete outcome data (attrition bias) | Low risk | LOCF<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Unclear risk | Not able to get study protocol |
| Vested interest bias | High risk | Funded by ALZA Corporation (medical company)<br>Conflicts of interest: Study authors are part of the Concerta Study Group |

### *Zeiner 1999*

| | |
|---|---|
| **Methods** | Cross-over trial with 2 interventions<br>1. Methylphenidate<br>2. Placebo<br>Phases: 7 weeks (3 weeks of medication, 1 week washout, 3 weeks of placebo)<br>Zeiner 1995 (in Zeiner 1999): extended treatment (mean duration 634 ± 130 days) |
| **Participants** | Number of participants screened: 46<br>Number of participants included: 38. Participants were randomly assigned to 1 of 2 possible drug condition orders<br>Number of participants followed up: 36 (36 boys, 0 girls)<br>Number of withdrawals: 2<br>Diagnosis of ADHD: DSM-III-R or DSM-IV (combined type (> 75%), hyperactive-impulsive and inattentive types not stated)<br>Age: mean 8,7 years (range 7 to 11)<br>IQ: mean 102 (range 79 to 139)<br>Methylphenidate naive: 100%<br>Ethnicity: not stated<br>Country: Norway<br>Setting: out-patient clinic<br>Comorbidity: oppositional defiant disorder (23; 64%)<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Male<br>2. Between 7 and 12 years of age<br>3. Fulfilled diagnostic criteria for ADHD<br>4. IQ ≥ 70<br>**Exclusion criteria**<br>1. Pervasive developmental disorder<br>2. Psychosis or mood disorder<br>3. Any acute or chronic medical or neurological disease<br>4. Used stimulants or any other psychotropic drug |
| **Interventions** | Participants were randomly assigned to 1 of 2 possible drug condition orders of methylphenidate (0.5 mg/kg) and placebo. Thirty-one children received a morning dose of 10 mg or 15 mg (and 5 young boys received 7.5 mg)<br>Mean methylphenidate dosage: not stated; 0.55 mg/kg to 0.56 mg/kg daily across the entire duration of the extended treatment period (Zeiner 1995 in Zeiner 1999)<br>Administration schedule: Capsules were given in 2 doses (at 8 AM and 11.30 AM)<br>Duration of each medication condition: 3 weeks<br>Washout before study initiation: not relevant<br>Methylphenidate naive: all<br>Medication-free period between interventions: 1 week<br>Titration period: none<br>Treatment compliance: no information |

| | |
|---|---|
| Outcomes | **ADHD symptoms**<br>1. Parent Account of Childhood Symptoms, at home<br>2. Conners' Teacher Rating, in classroom<br>Assessments of the child were made during the last week of each trial period<br>**Non-serious adverse events**<br>1. Height, weight, heart rate, systolic blood pressure, diastolic blood pressure |
| Notes | Sample calculation: no<br>Ethics approval: no information<br>**Comment from study authors**<br>1. This study has obvious limitations. Sample size was limited, and heterogeneity was noted with regard to behavioural characteristics and test performance. This heterogeneity may conceal associations found in subgroups of children with ADHD. Boys between 7 and 11 years of age were chosen. They represent the majority of children admitted with hyperactivity and inattention, but boys of other age groups may show a different clinical picture<br>**Key conclusions of study authors**<br>1. Response to methylphenidate was examined in 36 boys, 7 to 11 years of age, with ADHD in a double-blind, placebo-controlled trial of cross-over design<br>2. Hyperactivity and conduct problems were significantly reduced during methylphenidate treatment<br>3. Stimulant medication was associated with improvement on tests of sustained attention, working memory and motor steadiness<br>4. When individual changes were studied, it was found that 83% showed significant improvement in their hyperactivity at home or at school, and for 60%, levels of hyperactive behaviour were within the normal range<br>5. High levels of hyperactivity at school at a relatively low age was a significant predictor of normalisation of hyperactivity in ≥ 1 setting. However, these predictors could classify correctly only 71% of children<br>6. In clinical practice, a trial with stimulants is indicated for children with ADHD who show symptoms that are sufficiently severe to cause impairment at home and at school<br>**Comments from review authors**<br>1. Generation of allocation sequence is unclear<br>2. No sample size calculation was performed<br>3. Number of screened patients is unclear<br>4. In Zeiner 1995 (in Zeiner 1999), this was written: No sociodemographic information<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: no<br>Email correspondence with study authors: May to June 2014. We emailed Dr. Zeiner on 05 May 2014 and 02 June 2014 but never received a reply |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Children were randomly allocated to receive methylphenidate first or placebo first |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding of participants and personnel (performance bias) | Low risk | "A randomized crossover, double-blind design with methylphenidate and placebo". Placebo and methylphenidate capsules that were used were identical, to ensure blindness to the drug condition |
| Blinding of outcome assessment (detection bias) | Low risk | "All raters were blind to the drug condition" |
| Incomplete outcome data (attrition bias) | High risk | "The report from a teacher during one of the periods was missing for one child. Owing to technical problems or unwillingness to participate data were missing on some of the test measures [which measured side effects] for a few children" (Zeiner 1995 in Zeiner 1999)<br>Selection bias: yes; only responders from the 7-week trial were included in the extended-treatment methylphenidate group |
| Selective reporting (reporting bias) | Low risk | No selective outcome reporting |
| Vested interest bias | Low risk | This research was supported by the Norwegian Medical Research Council, the Norwegian Public Health Association and the Legacy of Haldis and Josef Andresen<br>Conflicts of interest: not declared |

*Zeni 2009*

| Methods | Randomised, cross-over trial with 2 interventions<br>1. Methylphenidate and aripiprazole<br>2. Placebo and aripiprazole<br>Phases: 2; randomisation, cross-over |
|---|---|

| | |
|---|---|
| Participants | Number of participants screened: 30<br>Number of participants included: 16 (9 boys, 7 girls). Participants were randomly assigned to 1 of 2 possible drug condition orders<br>Number of participants followed up: 14<br>Number of withdrawals: 1<br>Diagnosis of ADHD: DSM-IV (inattentive (7.1%), hyperactive (14.3%), combined (78.6%), out of n = 14)<br>Age: mean 10.71 years (SD 1.86; range 8 to 17)<br>IQ: > 70<br>Methylphenidate-naive: not stated<br>Ethnicity: European-Brazilian (71.4%), other (28.6%)<br>Country: Brazil<br>Setting: out-patient clinic<br>Co-morbidity: bipolar disorder (71.4%), borderline personality disorder (28.6%), anxiety disorder (57.1%), conduct disorder (57.1%), oppositional defiant disorder (78.6%), psychosis (50%), out of n = 14<br>Co-medication: aripiprazole (100%)<br>Sociodemographics: divorced parents (57.1%); socioeconomic level A + B + C: 92.9%; D + E: 7.1%<br>**Inclusion criteria**<br>1. 8 to 17 years of age<br>2. Diagnosis of borderline personality disorder, Axis I or II, co-morbid with ADHD (DSM-IV)<br>3. ADHD symptom onset preceding mood symptoms<br>4. ≥ 30% improvement in mood symptoms in previous trial of aripiprazole<br>5. Residual attention hyperactivity and opposition symptoms defined as score > 1.5 on the Swanson, Nolan and Pelham Scale, Fourth Edition<br>**Exclusion criteria**<br>1. IQ < 70<br>2. Use of any medication other than aripiprazole 10 weeks before the study<br>3. Diagnoses of pervasive developmental disorder<br>4. Schizophrenia<br>5. Substance abuse or dependence<br>6. Severe suicide/homicide risk counterindicating out-patient treatment<br>7. History of hypersensitivity to aripiprazole or methylphenidate<br>8. Any other acute or chronic disease that may interfere with the study<br>9. Pregnancy |
| Interventions | Participants were randomly assigned to different possible drug condition orders of methylphenidate (0.3 mg/kg for the first week, 0.7 mg/kg for the second week) and placebo, both alongside aripiprazole<br>Mean methylphenidate dosage: 15 mg in the first week (10 mg in the morning and 5 mg in the afternoon), 35 mg in the second week (20 mg in the morning and 15 mg in the afternoon)<br>Administration schedule: b.i.d. (morning and afternoon)<br>Duration of each medication condition: 2 weeks<br>Washout before study initiation: none (but recruited from 6-week aripiprazole study)<br>Medication-free period between interventions: not stated<br>Titration period: none<br>Treatment compliance: self report, mother's report, pill counting in returned blister packs |

| | |
|---|---|
| Outcomes | **ADHD symptoms**<br>1. Swanson, Nolan and Pelham Scale, Fourth Edition (Brazilian Version): rated weekly by parents<br>**General behaviour**<br>1. Oppositional index of the Swanson, Nolan and Pelham Scale, Fourth Edition (Brazilian Version): rated weekly by parents<br>**Non-serious adverse events**<br>1. Serious Adverse Event Rating Scale (SAERS)<br>2. Open question |
| Notes | Sample calculation: no<br>Ethics approval: yes<br>**Comments from study authors**<br>1. The small sample size may not have allowed us to detect significant differences between placebo and methylphenidate<br>2. The short-term duration of this trial may be an important limitation for the observation of significant differences in adverse events between therapeutic agents<br>**Key conclusions of study authors**<br>1. Methylphenidate was not more effective than placebo in reducing attention or hyperactivity symptoms in this short-term trial<br>2. Secondary finding suggests that depressive symptoms can be ameliorated by the addition of methylphenidate to aripiprazole<br>3. Although methylphenidate was found to not de-stabilise borderline personality disorder, its use should be considered with caution because 1 participant presented a severe mixed episode needing hospitalisation during methylphenidate treatment<br>Exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate before randomisation: Only participants who reported improved borderline personality disorder in the previous aripiprazole trial were included. However, participants who reported that ADHD improved too much (as indicated by a score < 1.5 on the Swanson, Nolan, and Pelham Scale, Fourth Edition) in the previous aripiprazole trial were excluded (see 'Exclusion criteria')<br>Any withdrawals due to adverse events: 1; exacerbation of borderline personality disorder and ADHD requiring hospitalisation<br>Email correspondence with study authors: May 2014. We obtained supplemental information regarding data. Study authors provided us with data from the first period |

Risk of bias table

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | An independent third party randomly assigned participants to groups A and B |
| Allocation concealment (selection bias) | Low risk | A pharmacist packaged methylphenidate and matching placebo in capsules, so they could not be differentiated by shape, colour, smell, weight or taste |
| Blinding of participants and personnel (performance bias) | Low risk | A pharmacist packaged methylphenidate and matching placebo in capsules, so they could not be differentiated by shape, colour, smell, weight or taste |
| Blinding of outcome assessment (detection bias) | Low risk | After all 4 assessments were completed, study blinding was broken |
| Incomplete outcome data (attrition bias) | Low risk | Analyses of primary and secondary outcome measures were performed using a mixed-effects model (MEM) approach, which provides a flexible framework for analysis of repeated measures, while accounting for missing data (i.e. lost to follow-up)<br>Selection bias (e.g. titration after randomisation → exclusion): no |
| Selective reporting (reporting bias) | Low risk | Outcomes reported according to protocol |
| Vested interest bias | Unclear risk | This work was fully supported by research grants from Conselho Nacional de Desenvolvimento Cientifico e Tecnologico (CNPq, Brazil) (Grant 471761=03-6) and Hospital de Clinicas de Porto Alegre (GPPG 03-325). Aripiprazole was provided by Bristol-Myers Squibb without restriction<br>Conflicts of interest: stated, "this is an independent investigator trial". However some study authors have affiliations with medical companies |

*Footnotes*

ADD: attention deficit disorder.
ADD-H: attention deficit disorder with hyperactivity.
ADHD: attention deficit hyperactivity disorder.
b.i.d.: twice a day.
CNS: central nervous system.
DSM-III-R: *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*, Revised.
DSM-IV: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.
DSM-IV-TR: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*.
ECG: electrocardiogram.
EEG: electroencephalogram.
EKG: electrocardiogram.
FDA: Food and Drug Administration.
ITT: intention-to-treat.
LLC: limited liability company.
LOCF: last observation carried forward.
LTFU: loss to follow-up.
MedDRA: Medical Dictionary for Regulatory Activities.
MPH: methylphenidate.
MPT: methylphenidate trial.
MTA: Multimodal Treatment Study of Children With ADHD.
MTS: methylphenidate transdermal system.
NNTB: number needed to treat for an additional beneficial outcome.
OROS: Osmotic Release Oral System.
PTS: placebo transdermal system.
q.a.m.: every morning.
qd: once a day.
RCT: randomised controlled trial.
SD: standard deviation.
SODAS: spheroidal oral drug absorption system.

t.i.d.: three times a day.

## Characteristics of excluded studies

### *An 2013*

| | |
|---|---|
| Reason for exclusion | N = No information<br>Likely no relevant outcome for our review<br>Outcomes reported: Resting state brain function |

### *Anderson 2002*

| | |
|---|---|
| Reason for exclusion | N = 10 boys<br>Likely no relevant outcome for our review<br>Outcomes reported: Functional magnetic resonance relaxometry |

### *Barkley 1988a*

| | |
|---|---|
| Reason for exclusion | N = 28<br>Likely no relevant outcome for our review<br>Outcomes reported: Home Situations Questionnaire; Parenting Stress Index; Beck Depression Inventory |

### *Barkley 1997*

| | |
|---|---|
| Reason for exclusion | N = No information<br>Likely no relevant outcome for our review<br>Outcomes reported: "2 questionnaires"; "Electronic apparatus" |

### *Bart 2013*

| | |
|---|---|
| Reason for exclusion | N = 24<br>Likely no relevant outcome for our review<br>Outcomes reported: Movement Assessment Battery for Children – Second edition; Online Continuous Performance Test |

### *Bedard 2002*

| | |
|---|---|
| Reason for exclusion | N = 31<br>Likely no relevant outcome for our review<br>Outcomes reported: Response interference; Stroop Naming Speed |

### *Bedard 2003*

| | |
|---|---|
| Reason for exclusion | N = 59<br>Likely no relevant outcome for our review<br>Outcomes reported: Parent Interview for Child Symptoms; Teacher Telephone Interview–IV; Selective Stop-Signal Task |

### *Bedard 2004*

| | |
|---|---|
| Reason for exclusion | N = 26<br>Likely no relevant outcome for our review<br>Outcomes reported: Parent Interview for Child Symptoms; Teacher Telephone Interview–IV; Reading subtest/Wide Range Achievement Test - 3; Word Attack and Word Identification subtests of the Woodcock Reading Mastery; Test-Revised Cambridge Neuropsychological Testing Automated Battery |

*Bedard 2007*

| | |
|---|---|
| Reason for exclusion | N = 40<br>Likely no relevant outcome for our review<br>Outcomes reported: Working memory; Test of Word and Language Efficiency; Wide Range Achievement Test - 3; Woodcock-Johnson Tests of Achievement; Cambridge Neuropsychological Test Automated Battery (CANTAB) Spatial Span |

*Beery 1994*

| | |
|---|---|
| Reason for exclusion | N = 70<br>Likely no relevant outcome for our review<br>Outcomes reported: Behavioural management, behavioural disinhibition |

*Ben-Pazi 2006*

| | |
|---|---|
| Reason for exclusion | N = 55<br>Likely no relevant outcome for our review<br>Outcomes reported: Hastening phenomena |

*Bental 2008*

| | |
|---|---|
| Reason for exclusion | N = 25<br>Likely no relevant outcome for our review<br>Outcomes reported: Reading measures |

*Brown 1984b*

| | |
|---|---|
| Reason for exclusion | N = 20<br>Likely no relevant outcome for our review<br>Outcomes reported: Children's Checking Task |

*Buhrmester 1992*

| | |
|---|---|
| Reason for exclusion | N = 19<br>Likely no relevant outcome for our review<br>Outcomes reported: Prosocial behavior |

*Campbell 1996*

| | |
|---|---|
| Reason for exclusion | N = 30<br>Likely no relevant outcome for our review<br>Outcomes reported: Reactions time on Tachistoscopic Task |

*Carlson 1991*

| | |
|---|---|
| Reason for exclusion | N = 13<br>Likely no relevant outcome for our review<br>Outcomes reported: Reaction times; cognitive tasks |

*Carlson 1992*

| | |
|---|---|
| Reason for exclusion | N = 24<br>Likely no relevant outcome for our review<br>Outcomes reported: On task and disruptive behaviour; academic work completion and accuracy |

*Cox 2004b*

| | |
|---|---|
| Reason for exclusion | N = 6<br>Likely no relevant outcome for our review<br>Outcomes reported: Driving performance - measured by computer |

*Dawson 1998*

| | |
|---|---|
| Reason for exclusion | N = 13<br>Likely no relevant outcome for our review<br>Outcomes reported: Mirsky's proposed factors of attention: sustained attention, focus/execute, encode, and stability of attention |

*De Sonneville 1991*

| | |
|---|---|
| Reason for exclusion | N = 17<br>Likely no relevant outcome for our review<br>Outcomes reported: Specific attention function: sustained attention, information processing, response organization |

*DeVito 2008*

| | |
|---|---|
| Reason for exclusion | N = 21<br>Likely no relevant outcome for our review<br>Outcomes reported: Cambridge Gamble Task; measures of response inhibition and reflection-impulsivity on the Information Sampling Task |

*Evans 1986*

| | |
|---|---|
| Reason for exclusion | N = No information<br>Likely no relevant outcome for our review<br>Outcomes reported: Verbal memory and learning |

*Fox 2014*

| | |
|---|---|
| Reason for exclusion | N = 14<br>Likely no relevant outcome for our review<br>Outcomes reported: Memory tasks |

*Francis 2001*

| | |
|---|---|
| Reason for exclusion | N = 50<br>Likely no relevant outcome for our review<br>Outcomes reported: Story telling and story grammar analysis |

*Gan 1982*

| | |
|---|---|
| Reason for exclusion | N = 20<br>Likely no relevant outcome for our review<br>Outcomes reported: Performance on paired-associate learning task |

*Granger 1996*

| | |
|---|---|
| Reason for exclusion | N = 26<br>Likely no relevant outcome for our review<br>Outcomes reported: Social behaviour |

*Grizenko 2010*

| | |
|---|---|
| Reason for exclusion | N = 371<br>Likely no relevant outcome for our review<br>Outcomes reported: Academic behaviour; sustained attention; impulse inhibition control |

*Günther 2010*

| | |
|---|---|
| Reason for exclusion | N = 54<br>Likely no relevant outcome for our review<br>Outcomes reported: Sustained attention measured by computer attention tests |

*Halliday 1983*

| | |
|---|---|
| Reason for exclusion | N = No information<br>Likely no relevant outcome for our review<br>Outcomes reported: Event-related potentials |

*Hanisch 2004*

| | |
|---|---|
| Reason for exclusion | N = 45<br>Likely no relevant outcome for our review<br>Outcomes reported: Computerized attention tasks |

*Hazel-Fernandez 2006*

| | |
|---|---|
| Reason for exclusion | N = 19<br>Likely no relevant outcome for our review<br>Outcomes reported: Paired Associates Learning Task; Tower of Hanoi |

*Hinshaw 1989*

| | |
|---|---|
| Reason for exclusion | N = 25<br>Likely no relevant outcome for our review<br>Outcomes reported: Prosocial behavior |

### *Hinshaw 1993*

| | |
|---|---|
| Reason for exclusion | N = 22<br>Likely no relevant outcome for our review<br>Outcomes reported: Antisocial behaviour |

### *Humphries 1979*

| | |
|---|---|
| Reason for exclusion | N = 24<br>Likely no relevant outcome for our review<br>Outcomes reported: Maze-tracking performance |

### *King 2009a*

| | |
|---|---|
| Reason for exclusion | N = 75<br>Likely no relevant outcome for our review<br>Outcomes reported: Social information processing |

### *King 2009b*

| | |
|---|---|
| Reason for exclusion | N = 32<br>Likely no relevant outcome for our review<br>Outcomes reported: Laboratory provocation task: measuring hostile, instrumental, reactive, and proactive aggression |

### *Lange 2007*

| | |
|---|---|
| Reason for exclusion | N = 58<br>Likely no relevant outcome for our review<br>Outcomes reported: Reaction time; alertness; vigilance; divided attention |

### *Leitner 2007b*

| | |
|---|---|
| Reason for exclusion | N = 16<br>Likely no relevant outcome for our review<br>Outcomes reported: Gait; stride to stride variability, memory, visual-spatial, verbal, and attention domains |

### *Malone 1988*

| | |
|---|---|
| Reason for exclusion | N = 31<br>Likely no relevant outcome for our review<br>Outcomes reported: Word processing; reaction time; cognitive decision task |

### *Malone 1993*

| | |
|---|---|
| Reason for exclusion | N = 26<br>Likely no relevant outcome for our review<br>Outcomes reported: Impulsive responding |

### *Malone 1994*

| | |
|---|---|
| Reason for exclusion | N = 17<br>Likely no relevant outcome for our review<br>Outcomes reported: Right hemisphere dysfunction |

*Martin 2007*

| | |
|---|---|
| Reason for exclusion | N = 24<br>Likely no relevant outcome for our review<br>Outcomes reported: Depression; addiction rate; Continuous Performance Task; heart rate and blood pressure |

*Mehta 2004*

| | |
|---|---|
| Reason for exclusion | N = 14<br>Likely no relevant outcome for our review<br>Outcomes reported: Working memory |

*Milich 1989*

| | |
|---|---|
| Reason for exclusion | N = 26<br>Likely no relevant outcome for our review<br>Outcomes reported: Continuous Performance Task |

*Milich 1991*

| | |
|---|---|
| Reason for exclusion | N = 21<br>Likely no relevant outcome for our review<br>Outcomes reported: Task persistence |

*Novak 1995*

| | |
|---|---|
| Reason for exclusion | N = 16<br>Likely no relevant outcome for our review<br>Outcomes reported: Reaction time; visuospatial attention |

*O'Toole 1997*

| | |
|---|---|
| Reason for exclusion | N = 23<br>Likely no relevant outcome for our review<br>Outcomes reported: Non-verbal learning |

*Peeke 1984*

| | |
|---|---|
| Reason for exclusion | N = 9<br>Likely no relevant outcome for our review<br>Outcomes reported: Verbal information processing |

*Pelham 1985*

| | |
|---|---|
| Reason for exclusion | N = 29<br>Likely no relevant outcome for our review<br>Outcomes reported: Classroom academic and social behaviour |

### *Pelham 1990b*

| | |
|---|---|
| Reason for exclusion | N = 17<br>Likely no relevant outcome for our review<br>Outcomes reported: Attention during baseball game; on task behaviour; ability to answer question about the status of the game |

### *Pelham 1992*

| | |
|---|---|
| Reason for exclusion | N = 28<br>Likely no relevant outcome for our review<br>Outcomes reported: Self-reported attribution and evaluation of behaviour |

### *Pelham 1997*

| | |
|---|---|
| Reason for exclusion | N = 60<br>Likely no relevant outcome for our review<br>Outcomes reported: Performance, self-evaluation, persistence, and attributions on cognitive task |

### *Pelham 2001b*

| | |
|---|---|
| Reason for exclusion | N = 68<br>Likely no relevant outcome for our review<br>Outcomes reported: A large number of different measures of behaviour |

### *Rapport 1995*

| | |
|---|---|
| Reason for exclusion | N = 45<br>Likely no relevant outcome for our review<br>Outcomes reported: Paired Associates Learning Task |

### *Richardson 1988*

| | |
|---|---|
| Reason for exclusion | N = 42<br>Likely no relevant outcome for our review<br>Outcomes reported: Reading achievement |

### *Rubia 2003*

| | |
|---|---|
| Reason for exclusion | N = 13<br>Likely no relevant outcome for our review<br>Outcomes reported: Motor timing |

### *Sangal 2006*

| | |
|---|---|
| Reason for exclusion | N = 58<br>Likely no relevant outcome for our review<br>Outcomes reported: Auditory amplitude |

### *Sengupta 2008*

| | |
|---|---|
| Reason for exclusion | N = 188<br>Likely no relevant outcome for our review<br>Outcomes reported: Task oriented behaviour |

*Silk 2012*

| | |
|---|---|
| Reason for exclusion | N = No information<br>Likely no relevant outcome for our review<br>Outcomes reported: Neural substrates |

*Smith 2013*

| | |
|---|---|
| Reason for exclusion | N = 20<br>Likely no relevant outcome for our review<br>Outcomes reported: Functional magnetic resonance imaging |

*Solanto 1986*

| | |
|---|---|
| Reason for exclusion | N = 12<br>Likely no relevant outcome for our review<br>Outcomes reported: Attention during play measured by locomotor activity; Children's Checking Test; and fine motor control |

*Solanto 1997*

| | |
|---|---|
| Reason for exclusion | N = 22<br>Likely no relevant outcome for our review<br>Outcomes reported: Continuous Performance Test |

*Srinivas 1992*

| | |
|---|---|
| Reason for exclusion | N = 9<br>Likely no relevant outcome for our review<br>Outcomes reported: Sustained attention measured by computer attention tests |

*Strand 2012*

| | |
|---|---|
| Reason for exclusion | N = 17<br>Likely no relevant outcome for our review<br>Outcomes reported: Working memory |

*Stray 2009*

| | |
|---|---|
| Reason for exclusion | N = 25<br>Likely no relevant outcome for our review<br>Outcomes reported: Motor functions |

*Swanson 1993*

| | |
|---|---|
| Reason for exclusion | N = 26<br>Likely no relevant outcome for our review<br>Outcomes reported: Impulsive responding |

*Szobot 2003*

| | |
|---|---|
| Reason for exclusion | N = 36<br>Likely no relevant outcome for our review<br>Outcomes reported: Cerebral blood flow |

*Tannock 2000*

| | |
|---|---|
| Reason for exclusion | N = 47<br>Likely no relevant outcome for our review<br>Outcomes reported: Naming speed and academic measures |

*Teicher 2003*

| | |
|---|---|
| Reason for exclusion | N = 19<br>Likely no relevant outcome for our review<br>Outcomes reported: Computerized Contiuous Performance Test and functional magnetic resonance imaging |

*Teicher 2006*

| | |
|---|---|
| Reason for exclusion | N = 14<br>Likely no relevant outcome for our review<br>Outcomes reported: Rate-dependent behavioural effects |

*Teicher 2007*

| | |
|---|---|
| Reason for exclusion | N = 11<br>Likely no relevant outcome for our review<br>Outcomes reported: McLean Motion Attention Test |

*Tillery 2000*

| | |
|---|---|
| Reason for exclusion | N = 32<br>Likely no relevant outcome for our review<br>Outcomes reported: Auditory performance |

*Trommer 1991*

| | |
|---|---|
| Reason for exclusion | N = 44<br>Likely no relevant outcome for our review<br>Outcomes reported: Go-No-GO performance |

*Tsang 2012*

| | |
|---|---|
| Reason for exclusion | N = 134<br>Likely no relevant outcome for our review<br>Outcomes reported: Cognitive tasks; emotional functions |

*Tucha 2006*

| | |
|---|---|
| Reason for exclusion | N = 58<br>Likely no relevant outcome for our review<br>Outcomes reported: Reaction time tasks |

### *Verbaten 1994*

| | |
|---|---|
| Reason for exclusion | N = 12<br>Likely no relevant outcome for our review<br>Outcomes reported: Continuous Performance Test |

### *Waschbusch 2007*

| | |
|---|---|
| Reason for exclusion | N = 61<br>Likely no relevant outcome for our review<br>Outcomes reported: Academic oriented tasks |

### *Whalen 1987*

| | |
|---|---|
| Reason for exclusion | N = 24<br>Likely no relevant outcome for our review<br>Outcomes reported: Social behaviour |

*Footnotes*

## Characteristics of studies awaiting classification

### *Drtilkova 1997*

| | |
|---|---|
| Methods | RCT<br>14 days<br>Studied all aspects of methylphenidate, amphetaminil, mesocarb and placebo in a group of 118 children |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Article is written in Czech. We have not yet been able to have the article translated |

### *Short 2004*

| | |
|---|---|
| Methods | The purpose of this trial was to examine the efficacy of psychostimulant medication in a naturalistic sample of pre-school children. Researchers examined the benefits and side effects of methylphenidate and mixed amphetamine salts (Adderall) |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

*Footnotes*

RCT: randomised controlled trial.

## Characteristics of ongoing studies

### *Bottelier 2014*

| | |
|---|---|
| Study name | |
| Methods | 16-week, placebo-controlled RCT with methylphenidate in 100 medication-naive participants with ADHD |
| Participants | |
| Interventions | |
| Outcomes | |
| Starting date | |
| Contact information | |
| Notes | This article describes methods and design. We are awaiting additional publications |

*Gendron 2012*

| | |
|---|---|
| Study name | |
| Methods | Placebo-controlled trial of methylphenidate involving 30 medication-naive children with ADHD |
| Participants | |
| Interventions | |
| Outcomes | |
| Starting date | |
| Contact information | |
| Notes | Correspondence with trial authors in August 2013. Trial will be submitted for review over the next few months |

*NCT00483106*

| | |
|---|---|
| Study name | Clinical and pharmacogenetic study of attention deficit hyperactivity disorder (ADHD) |
| Methods | RCT |
| Participants | Children with ADHD, aged 6 to 12 years |
| Interventions | Ritalin and placebo |
| Outcomes | Conners' Global Index (CGI) |
| Starting date | |
| Contact information | Ridha Jobber, McGill University |
| Notes | |

*NCT02039908*

| | |
|---|---|
| Study name | Examining tolerance to CNS stimulants in ADHD |
| Methods | RCT |
| Participants | Children with ADHD, aged 6 to 12 years |
| Interventions | Methylphenidate |
| Outcomes | |
| Starting date | |
| Contact information | |
| Notes | |

*Nurmi 2013*

| | |
|---|---|
| **Study name** | Pharmacogenetics of growth effects complicating ADHD treatment ( *Neuropsychopharmacology*) |
| **Methods** | 8-week RCT: double-blind, randomised, placebo-controlled trial with 4 interventions and 16-month extension<br>1. Guanfacine<br>2. Dexmethylphenidate<br>3. Combination guanfacine + dexmethylphenidate (16-month)<br>4. Placebo<br>Phases: 8-week, double-blind; 16 months open |
| **Participants** | Number of participants screened: not stated<br>Number of participants included: 209 (sex not stated). Participants were randomly assigned to 1 of 4 possible drug condition orders<br>Number of participants followed up: 99<br>Number of withdrawals: not stated<br>Diagnosis of ADHD: not stated<br>Age: not stated<br>IQ: not stated<br>Methylphenidate naive: not stated<br>Ethnicity: not stated<br>Country: USA<br>Comorbidity: not stated<br>Comedication: not stated<br>Sociodemographics: not stated<br>**Inclusion criteria**<br>1. Not stated<br>**Exclusion criteria**<br>1. Not stated |
| **Interventions** | Participants were randomly assigned to 1 of 3 possible drug condition orders of dexmethylphenidate and placebo<br>Administration schedule: not stated<br>Duration of each medication condition: not stated<br>Washout before trial initiation: not stated<br>Medication-free period between interventions: not stated<br>Titration period: not stated<br>Treatment compliance: not stated |
| **Outcomes** | **Outcomes:** adverse events<br>Both dexmethylphenidate monotherapy (Z-score decrease of -0.12 for height and -0.84 for BMI) and combination treatment (Z-score decrease of -0.19 for height and -0.83 for BMI) were associated with slowing of growth. In the methylphenidate-only condition, DRD3 rs3732790 minor allele homozygotes showed a 2.0 greater Z-score weight loss than was seen with common allele carriers (P value = $1.09 \times 10^{-8}$) |
| **Starting date** | 2012 (date on which conference abstract published). Study end date unknown |

| | |
|---|---|
| **Contact information** | Erika L Nurmi: erika.nurmi@vanderbit.edu<br>James T McCracken: jmcracken@mednet.ucla.edu. Department of Psychiatry and Biobehavioral Sciences, UCLA NPI-Semel Institute, 760 Westwood Plaza, Los Angeles, CA 90024-1759, USA |
| **Notes** | Sample calculation: no<br>Ethics approval: not stated<br>Results of this trial have not yet been published. Trial authors expect to publish their findings within the year |

*Footnotes*

ADHD: Attention deficit hyperactivity disorder.
BMI: Body mass index.
CNS: Central nervous system.
RCT: randomised controlled trial.

# Summary of findings tables

## 1 Methylphenidate compared with placebo or no intervention for ADHD

**Methylphenidate compared with placebo or no intervention for ADHD**

**Patient or population:** children and adolescents (up to and including 18 years of age) with ADHD
**Settings:** out-patient clinic, in-patient hospital ward and summer school
**Intervention:** methylphenidate
**Comparison:** placebo or no intervention

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | Number of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Placebo or no intervention | Methylphenidate | | | | |
| **ADHD symptoms: all parallel-group trials and first-period cross-over trials** ADHD Rating Scale (Teacher-rated)<br>Average study duration: 74.8 days | | Mean ADHD symptom score in the intervention groups corresponds to a mean difference of 9.6 (95% CI 11.25 to 8.00) on ADHD Rating Scale | **SMD -0.77** (-0.90 to -0.64) | 1698 (19 studies) | ⊕⊖⊖⊖ **Very low** a,b | The analysis was conducted on a standardised scale with data from studies that used different teacher-rated scales of symptoms (Conners' Teacher Rating Scale (CTRS), Strengths and Weaknesses of ADHD Symptoms and Normal Behaviour (SWAN) Scale, Schedule for Non-adaptive and Adaptive Personality (SNAP) - Teacher, Fremdbeurteilungsbogen für Hyperkinetische Störungen (FBB-HKS)). The effect size has been translated on to the ADHD Rating Scale from the SMD |
| **Total number of serious adverse events** | **Trial population** | | **RR 0.98** (0.44 to 2.22) | 1532 (9 studies) | ⊕⊖⊖⊖ **Very low** a,c | - |
| | **16 per 1000** | **16 per 1000** (7 to 36) | | | | |
| **Total number of non-serious adverse events** | **Trial population** | | **RR 1.29** (1.10 to 1.51) | 3132 (21 studies) | ⊕⊖⊖⊖ **Very low** a,b | - |
| | **408 per 1000** | **526 per 1000** (448 to 615) | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **General behaviour: all parallel-group trials and first-period cross-over trials** General behaviour rating scales (Teacher-rated) | | Mean general behaviour score in the intervention groups was **0.87 standard mean deviations lower** (95% CI 1.04 to 0.71 lower) | **SMD -0.87** (-0.71 to -1.04) | 668 (5 studies) | ⊕⊖⊖⊖ **Very low** a,d | - |
| **Quality of life** (Parent-rated) | | Mean quality of life score in the intervention groups corresponds to a mean difference of 8.0 (95% CI 5.49 to 10.46) on the Child Health Questionnaire | **SMD 0.61** (0.42 to 0.80) | 514 (3 studies) | ⊕⊖⊖⊖ **Very low** a,e | - |

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**ADHD:** Attention deficit hyperactivity disorder; **CI:** Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

GRADE Working Group grades of evidence.
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

*Footnotes*

[a]Downgraded two levels due to high risk of bias (systematic errors causing overestimation of benefits and underestimation of harms) in several risk of bias domains, including lack of sufficient blinding and selective outcome reporting (many of the included trials did not report on this outcome).

[b]Downgraded one level due to inconsistency: moderate statistical heterogeneity.

[c] Downgraded one level due to imprecision: wide confidence intervals.

[d]Downgraded one level due to indirectness: children's general behavior was assessed by different types of rating scales with different focus on behavior.

e Downgraded one level due to indirectness: children's quality of life was assessed by their parents.

# Additional tables

## 1 ADHD symptoms - rating scales

| Name of scale | Abbreviation | Reference |
|---|---|---|
| Abbreviated Conners' Rating Scales, Parent (ACPRS) and Teacher (ACTRS),<br>including Abbreviated Parent Rating Scale (APRS) and Teacher Rating Scale, Hyperkinesis Index and ADHD and Emotional Lability subscales | ACRS | Conners 1997a |
| Abbreviated Symptom Questionnaire, including ASQ Teacher and ASQ Parent | ASQ | Conners 1995 |
| Academic Performance Rating Scale | APRS | DuPaul 1991a |
| The ADD/H Comprehensive Teacher Rating Scale | ACTeRS | Ullmann 1984 |
| ADHD/ODD Rating Scale, Parent- and Teacher-Rated | ADHD-RS | Barkley 1998 |
| ADHD Rating Scale, including ADHD Rating Scale Parent and Teacher Ratings | ADHD-RS | DuPaul 1991a |

| Name of scale | Abbreviation | Reference |
|---|---|---|
| ADHD Rating Scale-IV, including ADHD Rating Scale-IV Parent and Teacher Versions | ADHD-RS-IV | DuPaul 1991a |
| Brief Psychiatric Rating Scale for Children | BPRS | Gale 1986 |
| Child Attention Problems Rating Scale | CAP | Achenbach 1986 |
| Child Attention Profile | CAP | Barkley 1988b |
| Child Behavior Rating Form | NCBHF | Aman 1996 |
| Child Symptom Inventory | CSI | Gadow 1994 |
| Children's Psychiatric Rating Scale | CPRS | Pfefferbaum-Levine 1983 |
| Conners' Abbreviated Hyperactivity Questionnaire | C-HI | Conners 1997a |
| Conners' Abbreviated Questionnaire | ASQ | Conners 1995 |
| Conners' Abbreviated Parent Teacher Questionnaire | APTQ | Rowe 1997 |
| Conners' Abbreviated Rating Scale | ABRS | Conners 1997a |
| Conners' Abbreviated Symptom Questionnaire | ASQ | Conners 1995 |
| Conners Abbreviated Symptom Questionnaire for Parents | ASQ-Parent | Conners 1995 |
| Conners' Abbreviated Symptom Questionnaire for Teachers | ASQ-Teacher | Conners 1997a |
| Conners' Abbreviated Teacher Rating Scale | ABTRS | Conners 2001 |
| Conners' ADHD/DSM-IV Scales Adolescent | CADS-A | Conners 1997b |
| Conners' ADHD/DSM-IV Scales Parent | CADS–P, CADS-P DSM-IV | Conners 1997a |
| Conners' ADHD/DSM-IV Scale Teacher, including Inattentive and Hyperactive-Impulsive subscales | CADS-T, CADS-T DSM-IV | Conners 1997a |
| Conners' Rating Scale - Revised, Parent and Teacher: Hyperactivity and Conduct Factors score | CPRS-R and CTRS-R | Goyette 1978 |
| Conners' Hyperactivity Index, Parent and Teacher, including abbreviated versions | CPRS/CTRS-Hyperactivity index | Conners 1997a |
| Conners' Hyperkinesis Index | - | Milich 1980 |
| Conners, Loney and Milich Scale | CLAM | Milich 1980 |
| Conners' Parent and Teacher Rating Scale - Revised, Short Form | CRS-R:S | Conners 1997a |
| Conners' Parent Rating Scale, including abbreviated versions | CPRS | Conners 1998b |
| Conners' Parent Rating Scale - Revised | CPRS-R | Conners 1997a |
| Conners' Parent Rating Scale - Revised, Short Form | CPRS-R:S | Conners 1997a |
| Conners' Parent Rating Scale - Revised, Long Version | CPRS-R:L | Conners 1997a |
| Conners' Rating Scale - Revised | CRS-R | Conners 1997a |
| Conners' Short Form Rating Scale, Parent and Teacher | - | Conners 1997a |
| Conners' Teacher Rating Scale | CTRS | Conners 1998a |
| Conners' Teacher Rating Scale - Revised, Long Version | CTRS-R:L | Conners 1998a |
| Diagnostic and Statistical Manual of Mental Disorders Total | DSM-IV | APA 1994 |
| Diagnostiksystem für Psychische Störungen im Kindes - und Jugendalter nach ICD-10 und DSM-IV,<br>Parental Questionnaire of ADHD symptoms | DISYPS | Döpfner 2000 |
| Fremdbeurteilungsbogen für Hyperkinetische Störungen | FBB-HKS | Döpfner 2008 |
| German Teacher's report on ADHD symptoms | FBB-HKS of the DISYPS | Döpfner 2000 |
| Hyperactivity Index of the Revised Conners Parent and Teacher Rating Scales | - | Goyette 1978 |
| IOWA Conners Parent Rating Scale, including abbreviated versions | IOWA CPRS | Loney 1982 |

| Name of scale | Abbreviation | Reference |
|---|---|---|
| IOWA Conners Teacher Rating Scale, including abbreviated versions | IOWA CTRS | Loney 1982 |
| IOWA Conners Teacher Rating Scale, Inattention/Overactivity (I/O) and Oppositional/Defiant (O/D) subscales | IOWA-I/O and O/D subscales | Loney 1982 |
| IOWA Inattention/Overactivity and Aggression/Noncompliance scales - Parent and Teacher rating | IOWA | Loney 1982 |
| Lehrer-Fragenbogen von Steinhausen | LF | Steinhausen 1993 |
| Loney's Time on Task Scale, Hyperactivity, Attention and Aggression subscales | TOTS | Fitzpatrick 1992b |
| Modified Conner Scale Parent and Teacher | ACR | Conners 1997a |
| Mothers' Objective Method for Subgrouping | MOMS | Loney 1984 |
| Parent Symptom Checklist | PSC ADHD | Döpfner 2000 |
| Parental Account of Children's Symptoms | PACS | Chen 2006 |
| Restricted Academic Situation Scale | RASS | Fischer 1998 |
| Schedule for Affective Disorders and Schizophrenia | K-SADS/ K-SADS-E for diagnosis | Chambers 1985 |
| Schedule for Non-adaptive and Adaptive Personality | SNAP | Clark 1993; Clark 1996 |
| Swanson, Nolan, and Pelham - IV SNAP-ADHD Rating scale | SNAP-ADHD | Swanson 1992 |
| Swanson, Nolan, and Pelham - IV SNAP-IV (Brazilian Version) | SNAP-IV | Clark 1993; Clark 1996 |
| Swanson, Kotkin, Atkins, M-Flynn, Pelham Scale (SKAMP combined, SKAMP attention, and SKAMP deportment) | SKAMP (SKAMP combined, SKAMP attention, and SKAMP deportment) | Wigal 1998; Murray 2009 |
| Teacher Self-control Rating Scale | SCRS | Kendall 1979 |
| Turgay - DSM-IV Scale, Parent | T-DSM-IV Scale, Parent | Turgay 1994; Ercan 2001 |
| Turgay - DSM-IV Scale, Teacher | T-DSM-IV Scale, Teacher | Turgay 1994; Ercan 2001 |
| Teacher Hyperactivity Index | THI | Achenbach 1991b |
| Teacher Symptom Checklist | TSC | Döpfner 2000 |
| Vanderbilt ADHD Rating Scale | VADP(T)RS | Wolraich 2003 |
| Wender Utah Rating Scale | WURS | Ward 1993 |
| Wide Range Achievement Test | WRAT-4 | Wilkinson 2006 |
| Wide Range Achievement Test Revised | WRAT-R | Woodcock 2001 |

*Footnotes*

ADD/H: Attention deficit disorder with hyperactivity.
ADHD: Attention deficit hyperactivity disorder.
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.
ODD: Oppositional defiant disorder.

## 2 Table 2: General behaviour rating scales

| Name of scale | Abbreviation | Reference |
|---|---|---|
| Achenbach Child Behaviour Checklist | CBCL | Achenbach 1991a |
| Achenbach's Teacher Report | ATRF | Achenbach 1991b; Achenbach 2001 |
| ADHD Rating Scale | ADHD-RS | DuPaul 1991a |
| ADHD School Observation Code | ADHD-SOC | Gadow 1996 |

| Name of scale | Abbreviation | Reference |
|---|---|---|
| Barkley Scales, Disruptive Behavior Disorders Rating Scale | - | Barkley 1991a |
| Child Attention Problems Scale | CAP | Barkley 1991 |
| Child Attention Profile | CAP | Barkley 1988b |
| Child Behavior Checklist | CBCL | Achenbach 1991a |
| Child Health Questionnaire | CHQ | Landgraf 1998 |
| Child and Adolescent Psychiatric Assessment, selected items | CAPA | Angold 1995 |
| Children's Psychiatric Rating Scale | CPRS | Fish 1985 |
| Classroom Observation Code (Abikoff Classroom Observational System) | COC | Abikoff 1980 |
| Code for Observing Social Activity | COSA | Sprafkin 1986 |
| Conners' Child Behavior Scale | UC-CCBS | Ladd 1996 |
| Conners' Global Index Scale | CGI-S | Conners 1998a |
| Conners' Global Index - Parent | CGI-P | Conners 1997a |
| Conners' Global Index - Teacher | CGI-T | Conners 1998a |
| Conners', Loney and Milich Scale | CLAM | Milich 1980 |
| Conners' Parent Questionnaire | CPQ | Conners 1995 |
| Conners' Parent Rating Scale | CPRS | Conners 1998b |
| Conners' Teacher Rating Scale | CTRS | Conners 1998a |
| Conners' Teacher Rating Conduct Problems | - | Miller 1997 |
| Disruptive Behavior Disorders Rating Scale, Parent- and Teacher-Rated | DBS | Mendelsohn 1978 |
| Disruptive Behavior Disorders Rating Scale | DBD | Silva 2005b |
| Groninger Behaviour Observation Scale | GOO and GBO | Van der Meere 1999b |
| Groninger Behaviour Checklists, Parent and Teacher Versions of the abbreviated Groninger | GGGS and GGBS | Van der Meere 1999b |
| Hillside Behavior Rating Scale | HBRS | Gittleman-Klein 1976 |
| Home Situations Questionnaire | HSQ | Barkley 1987 |
| Home Situations Questionnaire - Revised | HSQ-R | DuPaul 1992 |
| Humphrey's Teacher Self-Control Rating Scale | TSCRS | Humphrey 1982 |
| Hyperactivity Index from the Conners Revised Teacher Rating Scale | CTRS-R-Hyperactivity Index | Goyette 1978 |
| Impairment Rating Scale | IRS | Fabiano 2006 |
| Inpatient Global Rating Scale, Revised | IGRS | Conners 1985 |
| Inpatient Global Rating Scale, Somatic factor | IGRS-S | Conners 1985 |
| IOWA Conners' Rating Scale, Oppositional/Defiant (O/D) subscales | IOWA-O/D subscales | Loney 1982 |
| Nisonger Child Behavior Rating Form | NCBRF | Aman 1996 |
| Paired Associates Learning | PAL | Wechsler 1945 |
| Parent Global Assessment for Improvement | PGA | McGough 2006a |
| Peer Conflict Scale | PCS | Marsee 2007 |
| Personality Inventory for Children | PIC | Lachar 1986 |
| School Situations Questionnaire | SSQ | Barkley 1987 |
| School Situations Questionnaire - Revised | SSQ-R | DuPaul 1992 |
| Schedule for Nonadaptive and Adaptive Personality | SNAP | Clark 1993; Clark 1996 |

| Name of scale | Abbreviation | Reference |
|---|---|---|
| Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Scale, Parent and Teacher | SWAN | Swanson 2006; Polderman 2007 |
| Subjective Treatment Emergent Symptom Scale | STESS-R | Guy 1976 |
| Swanson, Nolan and Pelham, Fourth Edition | SNAP-IV | Bussing 2008 |
| Teachers Report Form | TRF | Achenbach 1991b |
| Telephone Interview Probe (Parent and Teacher) | TIP | Corkum 2007 |
| Vanderbilt ADHD rating scales: Vanderbilt ADHD Diagnostic Parent Rating Scale and Vanderbilt ADHD Diagnostic Teacher Rating Scale | VADPRS and VADTRS | Wolraich 2003 |
| Wahler, House and Stambaugh's Ecobehavioral Assessment System | ECO | Wahler 1976 |
| The Weekly Parent Ratings of Evening and Morning Behaviour | WREMB-R | Kelsey 2004 |
| Werry-Weiss-Peters Activity Rating Scale | WWP | Routh 1978 |
| Woodcock-Johnson Achievement Battery | WJ-III Ach | Woodcock 2001 |

*Footnotes*

ADHD: attention deficit hyperactivity disorder.

### 3 Table 3: Quality of life ratings scales

| Name of scale | Abbreviation | Reference |
|---|---|---|
| ADHD Impact Module-Child | AIM-C | AIM-C 2013 |
| Child Impact Scale and Home Impact Scale | CIS/HIS | Landgraf 2002 |
| Child Health and Illness Profile, Child Edition: Parent Report Form | CHIP-CE:PRF | Riley 2004 |
| Child Health Questionnaire | CHQ-P | Landgraf 1998 |
| Children's Global Assessment Scale | CGAS | Shaffer 1983 |
| Comprehensive Psychopathological Rating Scale | CPRS | Aasberg 1978 |
| Health Utilities Index - 2 | HUI-2 | Torrance 1982 |

*Footnotes*

ADHD: attention deficit hyperactivity disorder.

## References to studies

### Included studies

#### *Abikoff 2009*

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Concerta for organizational deficits in ADHD. The Brown University Child and Adolescent Behavior Letter 2009;25(3):2.

#### *Ahmann 1993*

Ahmann PA, Waltonen SJ, Olson KA, Theye FW, Van Erem AJ, LaPlant RJ. Placebo-controlled evaluation of Ritalin side effects. Pediatrics 1993;91(6):1101-6.

#### *Armstrong 2012*

* Armstrong RB, Damaraju CV, Ascher S, Schwarzman L, O'Neill J, Starr HL. Time course of treatment effect of OROS® methylphenidate in children with ADHD. Journal of Attention Disorders 2012;16(8):697-705.

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Wigal SB, Wigal T, Schuck S, Brams M, Williamson D, Armstrong RB, et al. Academic, behavioral, and cognitive effects of OROS® methylphenidate on older children with attention-deficit/hyperactivity disorder. Journal of Child and Adolescent Psychopharmacology 2011;21(2):121-31.

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#### *Arnold 2004*

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### *Barkley 1991*

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### *Barkley 2000*

Barkley RA, Connor DF, Kwasnik D. Challenges to determining adolescent medication response in an outpatient clinical setting: comparing Adderall and methylphenidate for ADHD. Journal of Attention Disorders 2000;4(2):102-13.

### *Bedard 2008*

Bedard A-C, Tannock R. Anxiety, methylphenidate response, and working memory in children with ADHD. Journal of Attention Disorders 2008;11(5):546-57.

### *Ben 2002*

Ben AL, Grizenko N, Mbekou V, Lageix P, Baron C, Schwartz G, et al. Dopamine transporter gene and behavioral response to methylphenidate (MPH) in children with attention deficit hyperactivity disorder (ADHD). In: American Journal of Medical Genetics. Abstracts of the Xth World Congress of Psychiatric Genetics; 2002 October 9-13; Brussels, Belgium. Vol. 114 (7). 2002:724-5.

### *Biederman 2003*

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### *Brams 2012*

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### *Brown 1985*

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### *Brown 1988*

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# Data and analyses

## 1 Teacher-rated ADHD symptoms

| Outcome or Subgroup | Studies | Participants | Statistical Method | Effect Estimate |
|---|---|---|---|---|
| 1.1 All parallel-group trials and first-period cross-over trials | 19 | 1698 | Std. Mean Difference(IV, Random, 95% CI) | -0.77[-0.90, -0.64] |
| 1.1.1 Low risk of bias | 0 | 0 | Std. Mean Difference(IV, Random, 95% CI) | Not estimable |
| 1.1.2 High risk of bias | 19 | 1698 | Std. Mean Difference(IV, Random, 95% CI) | -0.77[-0.90, -0.64] |
| 1.2 Subgroup analysis: types of scales | 19 | | Std. Mean Difference(IV, Random, 95% CI) | Subtotals only |
| 1.2.1 Conners' Teacher Rating Scale (CTRS) | 8 | 518 | Std. Mean Difference(IV, Random, 95% CI) | -0.64[-0.82, -0.47] |
| 1.2.2 Abbreviated Conners' Rating Scale (ACRS) - Teacher | 2 | 105 | Std. Mean Difference(IV, Random, 95% CI) | -0.75[-1.79, 0.29] |
| 1.2.3 Conners' Abbreviated Symptom Questionnaire for Teachers (ASQ-Teacher) | 1 | 59 | Std. Mean Difference(IV, Random, 95% CI) | -0.28[-0.79, 0.23] |
| 1.2.4 IOWA Conners' Teacher Rating Scale (IOWA CTRS) - hyperactivity | 2 | 193 | Std. Mean Difference(IV, Random, 95% CI) | -1.08[-1.39, -0.77] |
| 1.2.5 Schedule for Non-adaptive and Adaptive Personality (SNAP) - Teacher | 2 | 328 | Std. Mean Difference(IV, Random, 95% CI) | -0.61[-0.96, -0.25] |
| 1.2.6 Teacher ratings of attention | 1 | 20 | Std. Mean Difference(IV, Random, 95% CI) | -0.55[-1.45, 0.35] |
| 1.2.7 Teacher ratings of impulsivity | 1 | 20 | Std. Mean Difference(IV, Random, 95% CI) | 0.04[-0.83, 0.92] |
| 1.2.8 IOWA Conners' Teacher Rating Scale - Inattention/Overactivity (IOWA-I/O) | 2 | 197 | Std. Mean Difference(IV, Random, 95% CI) | -1.03[-1.36, -0.69] |
| 1.2.9 Fremdbeurteilungsbogen für Hyperkinetische Störungen (FBB-HKS) | 1 | 85 | Std. Mean Difference(IV, Random, 95% CI) | -1.06[-1.52, -0.61] |
| 1.2.10 Conners' ADHD/DSM-IV Scales - Teacher (CADS-T) | 2 | 254 | Std. Mean Difference(IV, Random, 95% CI) | -1.05[-1.31, -0.78] |
| 1.2.11 Strengths and Weaknesses of ADHD Symptoms and Normal Behaviour (SWAN) Scale | 1 | 64 | Std. Mean Difference(IV, Random, 95% CI) | -0.33[-0.82, 0.17] |
| 1.3 Medication status: medication naive versus not medication naive | 6 | 717 | Std. Mean Difference(IV, Random, 95% CI) | -0.79[-1.08, -0.50] |
| 1.3.1 Medication naive | 4 | 431 | Std. Mean Difference(IV, Random, 95% CI) | -0.63[-0.94, -0.31] |
| 1.3.2 Not medication naive | 2 | 286 | Std. Mean Difference(IV, Random, 95% CI) | -1.06[-1.33, -0.79] |
| 1.4 Subgroup analysis: duration of treatment | 19 | 1698 | Std. Mean Difference(IV, Random, 95% CI) | -0.77[-0.90, -0.64] |
| 1.4.1 Short term (up to 6 months) | 18 | 1445 | Std. Mean Difference(IV, Random, 95% CI) | -0.81[-0.94, -0.68] |
| 1.4.2 Long term (over 6 months) | 1 | 253 | Std. Mean Difference(IV, Random, 95% CI) | -0.47[-0.72, -0.22] |
| 1.5 Subgroup analysis: dose | 19 | | Std. Mean Difference(IV, Random, 95% CI) | Subtotals only |
| 1.5.1 Low dose | 8 | 493 | Std. Mean Difference(IV, Random, 95% CI) | -0.64[-0.82, -0.46] |
| 1.5.2 High dose | 7 | 688 | Std. Mean Difference(IV, Random, 95% CI) | -0.81[-1.08, -0.54] |
| 1.5.3 Unknown dose | 6 | 669 | Std. Mean Difference(IV, Random, 95% CI) | -0.87[-1.06, -0.68] |

| | | | | |
|---|---|---|---|---|
| 1.6 Subgroup analysis: parallel-group trials compared with first-period cross-over trials | 19 | 1698 | Std. Mean Difference(IV, Random, 95% CI) | -0.77[-0.90, -0.64] |
| 1.6.1 Parallel-group trials | 17 | 1506 | Std. Mean Difference(IV, Random, 95% CI) | -0.80[-0.95, -0.65] |
| 1.6.2 First-period cross-over trials | 2 | 192 | Std. Mean Difference(IV, Random, 95% CI) | -0.58[-0.87, -0.29] |
| 1.7 Subgroup analysis: trials with cohort selection bias of all participants compared with trials without cohort selection bias of all participants | 19 | 1698 | Std. Mean Difference(IV, Random, 95% CI) | -0.77[-0.90, -0.64] |
| 1.7.1 Trials with cohort selection bias of all participants | 7 | 994 | Std. Mean Difference(IV, Random, 95% CI) | -0.79[-1.01, -0.57] |
| 1.7.2 Trials without cohort selection bias of all participants | 12 | 704 | Std. Mean Difference(IV, Random, 95% CI) | -0.76[-0.93, -0.59] |
| 1.8 ADHD symptoms, cross-over trial (endpoint data) | 59 | 5145 | Std. Mean Difference(IV, Random, 95% CI) | -0.93[-1.06, -0.80] |
| 1.8.1 Low risk of bias | 4 | 204 | Std. Mean Difference(IV, Random, 95% CI) | -0.64[-0.97, -0.30] |
| 1.8.2 High risk of bias | 55 | 4941 | Std. Mean Difference(IV, Random, 95% CI) | -0.95[-1.09, -0.82] |
| 1.9 ADHD symptoms, cross-over trials (endpoint data), subgroup analysis: dose | 59 | 6821 | Std. Mean Difference(IV, Random, 95% CI) | -0.85[-0.96, -0.74] |
| 1.9.1 Low dose | 42 | 3408 | Std. Mean Difference(IV, Random, 95% CI) | -0.73[-0.89, -0.57] |
| 1.9.2 High dose | 36 | 3413 | Std. Mean Difference(IV, Random, 95% CI) | -0.98[-1.13, -0.84] |
| 1.10 Subgroup analysis: all parallel-group trials and first-period cross-over trials compared with cross-over trials (endpoint data) | 75 | 6344 | Std. Mean Difference(IV, Random, 95% CI) | -0.91[-1.01, -0.80] |
| 1.10.1 All parallel-group trials and first-period cross-over trials | 19 | 1698 | Std. Mean Difference(IV, Random, 95% CI) | -0.77[-0.90, -0.64] |
| 1.10.2 Cross-over trials (endpoint data) | 56 | 4646 | Std. Mean Difference(IV, Random, 95% CI) | -0.95[-1.09, -0.82] |
| 1.11 All parallel-group trials and cross-over trials: risk of bias | 75 | 6344 | Std. Mean Difference(IV, Random, 95% CI) | -0.91[-1.01, -0.80] |
| 1.11.1 Low risk of bias | 4 | 204 | Std. Mean Difference(IV, Random, 95% CI) | -0.64[-0.97, -0.30] |
| 1.11.2 High risk of bias | 71 | 6140 | Std. Mean Difference(IV, Random, 95% CI) | -0.92[-1.03, -0.81] |

## 2 Independent assessor-rated ADHD symptoms

| Outcome or Subgroup | Studies | Participants | Statistical Method | Effect Estimate |
|---|---|---|---|---|
| 2.1 All parallel-group trials and first-period cross-over trials | 10 | 1907 | Std. Mean Difference(IV, Random, 95% CI) | -0.64[-0.89, -0.39] |
| 2.1.1 Low risk of bias | 0 | 0 | Std. Mean Difference(IV, Random, 95% CI) | Not estimable |
| 2.1.2 High risk of bias | 10 | 1907 | Std. Mean Difference(IV, Random, 95% CI) | -0.64[-0.89, -0.39] |
| 2.2 Subgroup analysis: types of scales | 10 | | Std. Mean Difference(IV, Random, 95% CI) | Subtotals only |
| 2.2.1 Swanson, Kotkin, Agler, M-Glynn and Pelham (SKAMP) Scale | 1 | 164 | Std. Mean Difference(IV, Random, 95% CI) | -0.72[-1.04, -0.41] |
| 2.2.2 ADHD Rating Scale (ADHD-RS ) | 7 | 1442 | Std. Mean Difference(IV, Random, 95% CI) | -0.71[-1.09, -0.32] |
| 2.2.3 Swanson, Nolan and Pelham (SNAP) Scale | 1 | 221 | Std. Mean Difference(IV, Random, 95% CI) | -0.35[-0.61, -0.08] |
| 2.2.4 Unknown | 1 | 78 | Std. Mean Difference(IV, Random, 95% CI) | -0.94[-1.41, -0.47] |

| | | | | |
|---|---|---|---|---|
| 2.3 Subgroup analysis: duration of treatment | 10 | 1907 | Std. Mean Difference(IV, Random, 95% CI) | -0.64[-0.89, -0.39] |
| 2.3.1 Short term (up to 6 months) | 9 | 1686 | Std. Mean Difference(IV, Random, 95% CI) | -0.68[-0.95, -0.40] |
| 2.3.2 Long term (over 6 months) | 1 | 221 | Std. Mean Difference(IV, Random, 95% CI) | -0.35[-0.61, -0.08] |
| 2.4 Subgroup analysis: parallel-group trials compared with first-period cross-over trials | 10 | 1907 | Std. Mean Difference(IV, Random, 95% CI) | -0.64[-0.89, -0.39] |
| 2.4.1 Parallel-group trials | 7 | 1609 | Std. Mean Difference(IV, Random, 95% CI) | -0.60[-0.91, -0.28] |
| 2.4.2 First-period cross-over trials | 3 | 298 | Std. Mean Difference(IV, Random, 95% CI) | -0.76[-0.99, -0.52] |
| 2.5 Subgroup analysis: trials with cohort selection bias of all participants compared with trials without cohort selection bias of all participants | 10 | 1907 | Std. Mean Difference(IV, Random, 95% CI) | -0.64[-0.89, -0.39] |
| 2.5.1 Trials with cohort selection bias of all participants | 4 | 630 | Std. Mean Difference(IV, Random, 95% CI) | -0.51[-0.73, -0.29] |
| 2.5.2 Trials without cohort selection bias of all participants | 6 | 1277 | Std. Mean Difference(IV, Random, 95% CI) | -0.72[-1.11, -0.33] |
| 2.6 Subgroup analysis: dose | 10 | 1907 | Std. Mean Difference(IV, Random, 95% CI) | -0.64[-0.89, -0.39] |
| 2.6.1 Low dose | 0 | 0 | Std. Mean Difference(IV, Random, 95% CI) | Not estimable |
| 2.6.2 High dose | 6 | 1380 | Std. Mean Difference(IV, Random, 95% CI) | -0.55[-0.91, -0.20] |
| 2.6.3 Unknown dose | 4 | 527 | Std. Mean Difference(IV, Random, 95% CI) | -0.80[-0.98, -0.61] |
| 2.7 ADHD symptoms, cross-over trials (endpoint data), subgroup analysis: risk of bias | 19 | 2471 | Std. Mean Difference(IV, Random, 95% CI) | -1.00[-1.16, -0.84] |
| 2.7.1 Low risk of bias | 0 | 0 | Std. Mean Difference(IV, Random, 95% CI) | Not estimable |
| 2.7.2 High risk of bias | 19 | 2471 | Std. Mean Difference(IV, Random, 95% CI) | -1.00[-1.16, -0.84] |
| 2.8 ADHD symptoms, cross-over trials (endpoint data), subgroup analysis: dose | 19 | 3874 | Std. Mean Difference(IV, Random, 95% CI) | -0.89[-1.02, -0.75] |
| 2.8.1 Low dose | 16 | 2021 | Std. Mean Difference(IV, Random, 95% CI) | -0.69[-0.82, -0.55] |
| 2.8.2 High dose | 12 | 1853 | Std. Mean Difference(IV, Random, 95% CI) | -1.13[-1.31, -0.95] |
| 2.9 Subgroup analysis: all parallel-group trials and first-period cross-over trials compared with cross-over trials (endpoint data) | 28 | 4215 | Std. Mean Difference(IV, Random, 95% CI) | -0.83[-0.98, -0.67] |
| 2.9.1 All parallel-group trials and first-period cross-over trials | 10 | 1907 | Std. Mean Difference(IV, Random, 95% CI) | -0.64[-0.89, -0.39] |
| 2.9.2 Cross-over trials (endpoint data) | 18 | 2308 | Std. Mean Difference(IV, Random, 95% CI) | -0.95[-1.13, -0.77] |

### 3 Parent-rated ADHD symptoms

| Outcome or Subgroup | Studies | Participants | Statistical Method | Effect Estimate |
|---|---|---|---|---|
| 3.1 All parallel-group trials and first-period cross-over trials | 21 | 2187 | Std. Mean Difference(IV, Random, 95% CI) | -0.66[-0.82, -0.51] |
| 3.1.1 Low risk of bias | 0 | 0 | Std. Mean Difference(IV, Random, 95% CI) | Not estimable |
| 3.1.2 High risk of bias | 21 | 2187 | Std. Mean Difference(IV, Random, 95% CI) | -0.66[-0.82, -0.51] |

| | | | | |
|---|---|---|---|---|
| 3.2 Subgroup analysis: types of scales | 21 | | Std. Mean Difference(IV, Random, 95% CI) | Subtotals only |
| 3.2.1 Conners' Parent Rating Scale (CPRS) | 7 | 751 | Std. Mean Difference(IV, Random, 95% CI) | -0.58[-0.87, -0.30] |
| 3.2.2 ADHD Rating Scale - Fourth Edition (ADHD-RS-IV) | 2 | 194 | Std. Mean Difference(IV, Random, 95% CI) | -0.30[-0.58, -0.02] |
| 3.2.3 Fremdbeurteilungsbogen für Hyperkinetische Störungen (FBB-HKS) | 1 | 85 | Std. Mean Difference(IV, Random, 95% CI) | -0.91[-1.36, -0.46] |
| 3.2.4 Conners' ADHD/DSM-IV Scales - Parent (CADS-P) | 1 | 120 | Std. Mean Difference(IV, Random, 95% CI) | -1.26[-1.65, -0.86] |
| 3.2.5 CADS-P Inattentive subscale | 1 | 109 | Std. Mean Difference(IV, Random, 95% CI) | -0.78[-1.17, -0.39] |
| 3.2.6 CADS-P Hyperactivity subscale | 1 | 109 | Std. Mean Difference(IV, Random, 95% CI) | -0.93[-1.32, -0.53] |
| 3.2.7 Clinican's Manual for the Assesment of Disruptive Behavior Disorders Rating Scale for Parents (Barkley) | 1 | 41 | Std. Mean Difference(IV, Random, 95% CI) | -0.21[-0.82, 0.41] |
| 3.2.8 Abbreviated Conners' Rating Scale (ACRS) - Parent | 2 | 121 | Std. Mean Difference(IV, Random, 95% CI) | -0.62[-0.99, -0.25] |
| 3.2.9 Swanson, Nolan, and Pelham, Fourth Edition - Parent (SNAP-IV-Parent) Scale | 4 | 430 | Std. Mean Difference(IV, Random, 95% CI) | -0.60[-0.79, -0.40] |
| 3.2.10 Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) Scale | 1 | 86 | Std. Mean Difference(IV, Random, 95% CI) | -0.43[-0.86, 0.00] |
| 3.2.11 IOWA Conners' Rating Scale - Inattention/Overactivity (IOWA-I/O) | 3 | 352 | Std. Mean Difference(IV, Random, 95% CI) | -0.78[-1.35, -0.21] |
| 3.3 Subgroup analysis: duration of treatment | 21 | 2187 | Std. Mean Difference(IV, Random, 95% CI) | -0.66[-0.82, -0.51] |
| 3.3.1 Short term (up to 6 months) | 20 | 1925 | Std. Mean Difference(IV, Random, 95% CI) | -0.67[-0.84, -0.50] |
| 3.3.2 Long term (over 6 months) | 1 | 262 | Std. Mean Difference(IV, Random, 95% CI) | -0.58[-0.82, -0.33] |
| 3.4 Subgroup analysis: dose | 21 | 2335 | Std. Mean Difference(IV, Random, 95% CI) | -0.64[-0.79, -0.48] |
| 3.4.1 Low dose | 5 | 329 | Std. Mean Difference(IV, Random, 95% CI) | -0.53[-1.00, -0.07] |
| 3.4.2 High dose | 10 | 1132 | Std. Mean Difference(IV, Random, 95% CI) | -0.60[-0.86, -0.33] |
| 3.4.3 Unknown dose | 8 | 874 | Std. Mean Difference(IV, Random, 95% CI) | -0.72[-0.92, -0.52] |
| 3.5 Medication status: medication naive versus not medication naive | 7 | 795 | Std. Mean Difference(IV, Random, 95% CI) | -0.76[-1.05, -0.48] |
| 3.5.1 Medication naive | 4 | 492 | Std. Mean Difference(IV, Random, 95% CI) | -0.69[-1.03, -0.35] |
| 3.5.2 Not medication naive | 3 | 303 | Std. Mean Difference(IV, Random, 95% CI) | -0.88[-1.33, -0.42] |
| 3.6 Subgroup analysis: trials with cohort selection bias of all participants compared with trials without cohort selection bias of all participants | 21 | 2187 | Std. Mean Difference(IV, Random, 95% CI) | -0.66[-0.82, -0.51] |
| 3.6.1 Trials with selection bias of all participants | 10 | 1559 | Std. Mean Difference(IV, Random, 95% CI) | -0.68[-0.86, -0.51] |
| 3.6.2 Trials without cohort selection bias of all participants | 11 | 628 | Std. Mean Difference(IV, Random, 95% CI) | -0.62[-0.90, -0.33] |

| | | | | |
|---|---|---|---|---|
| 3.7 Subgroup analysis: parallel-group trials compared with first-period cross-over trials | 21 | 2187 | Std. Mean Difference(IV, Random, 95% CI) | -0.66[-0.82, -0.51] |
| 3.7.1 Parallel-group trials | 19 | 2094 | Std. Mean Difference(IV, Random, 95% CI) | -0.66[-0.83, -0.50] |
| 3.7.2 First-period cross-over trials | 2 | 93 | Std. Mean Difference(IV, Random, 95% CI) | -0.65[-1.07, -0.23] |
| 3.8 ADHD symptoms, cross-over trials (endpoint data) | 41 | 3734 | Std. Mean Difference(IV, Random, 95% CI) | -0.78[-0.90, -0.67] |
| 3.8.1 Low risk of bias | 4 | 204 | Std. Mean Difference(IV, Random, 95% CI) | -0.54[-0.96, -0.13] |
| 3.8.2 High risk of bias | 37 | 3530 | Std. Mean Difference(IV, Random, 95% CI) | -0.81[-0.92, -0.69] |
| 3.9 ADHD symptoms, cross-over trials (endpoint data), subgroup analysis: dose | 41 | 4918 | Std. Mean Difference(IV, Random, 95% CI) | -0.69[-0.79, -0.58] |
| 3.9.1 Low dose | 26 | 2272 | Std. Mean Difference(IV, Random, 95% CI) | -0.65[-0.82, -0.48] |
| 3.9.2 High dose | 28 | 2646 | Std. Mean Difference(IV, Random, 95% CI) | -0.72[-0.84, -0.60] |
| 3.10 Subgroup analysis: all parallel-group trials and first-period cross-over trials compared with cross-over trials (endpoint data) | 59 | 5861 | Std. Mean Difference(IV, Random, 95% CI) | -0.74[-0.83, -0.65] |
| 3.10.1 All parallel-group trials and first-period cross-over trials | 21 | 2215 | Std. Mean Difference(IV, Random, 95% CI) | -0.66[-0.82, -0.51] |
| 3.10.2 Cross-over trials (endpoint data) | 39 | 3646 | Std. Mean Difference(IV, Random, 95% CI) | -0.79[-0.90, -0.67] |

## 4 Additional subgroup analyses of ADHD symptoms: parallel-group trials and first-period cross-over trials

| Outcome or Subgroup | Studies | Participants | Statistical Method | Effect Estimate |
|---|---|---|---|---|
| 4.1 Comparision of raters | 31 | 5697 | Std. Mean Difference(IV, Random, 95% CI) | -0.69[-0.79, -0.59] |
| 4.1.1 Teacher-rated | 19 | 1689 | Std. Mean Difference(IV, Random, 95% CI) | -0.78[-0.93, -0.63] |
| 4.1.2 Independent assessor-rated | 9 | 1829 | Std. Mean Difference(IV, Random, 95% CI) | -0.61[-0.87, -0.35] |
| 4.1.3 Parent-rated | 21 | 2179 | Std. Mean Difference(IV, Random, 95% CI) | -0.65[-0.81, -0.50] |
| 4.2 Age | 6 | 1039 | Std. Mean Difference(IV, Random, 95% CI) | -0.44[-0.74, -0.14] |
| 4.2.1 2 to 6 years | 1 | 64 | Std. Mean Difference(IV, Random, 95% CI) | -0.33[-0.82, 0.17] |
| 4.2.2 7 to 11 years | 2 | 278 | Std. Mean Difference(IV, Random, 95% CI) | -0.59[-1.03, -0.15] |
| 4.2.3 12 to 18 years | 3 | 697 | Std. Mean Difference(IV, Random, 95% CI) | -0.38[-0.88, 0.12] |
| 4.3 Comorbidity versus no comorbidity | 20 | 2310 | Std. Mean Difference(IV, Random, 95% CI) | -0.72[-0.91, -0.53] |
| 4.3.1 ADHD with comorbidity | 18 | 1981 | Std. Mean Difference(IV, Random, 95% CI) | -0.72[-0.94, -0.51] |
| 4.3.2 ADHD without comorbidity | 2 | 329 | Std. Mean Difference(IV, Random, 95% CI) | -0.69[-0.92, -0.46] |
| 4.4 Subtypes ADHD: ADHD Rating Scale (parent-, teacher- or independent assessor-rated) | 2 | | Std. Mean Difference(IV, Random, 95% CI) | Subtotals only |
| 4.4.1 Combined ADHD | 2 | 559 | Std. Mean Difference(IV, Random, 95% CI) | 0.65[-1.30, 2.60] |
| 4.4.2 Inattentive ADHD | 1 | 204 | Std. Mean Difference(IV, Random, 95% CI) | -1.31[-1.61, -1.01] |

| | | | | |
|---|---|---|---|---|
| 4.5 Cross-over trials: first-period data versus endpoint data (parent-, independent assessor- and teacher-rated) | 4 | | Std. Mean Difference(IV, Random, 95% CI) | Subtotals only |
| 4.5.1 First-period data | 4 | 372 | Std. Mean Difference(IV, Random, 95% CI) | -0.64[-0.85, -0.44] |
| 4.5.2 Endpoint data | 4 | 372 | Std. Mean Difference(IV, Random, 95% CI) | -0.91[-1.18, -0.65] |

### 5 Number of serious adverse events: parallel-group trials and first-period cross-over trials

| Outcome or Subgroup | Studies | Participants | Statistical Method | Effect Estimate |
|---|---|---|---|---|
| 5.1 Number of serious adverse events (SAE) | 9 | 1532 | Risk Ratio(IV, Random, 95% CI) | 0.98[0.44, 2.22] |
| 5.2 Nervous system | 6 | 2280 | Risk Ratio(IV, Random, 95% CI) | 0.87[0.30, 2.53] |
| 5.2.1 Aggression | 1 | 303 | Risk Ratio(IV, Random, 95% CI) | 0.50[0.05, 5.49] |
| 5.2.2 Concussion | 1 | 303 | Risk Ratio(IV, Random, 95% CI) | 0.34[0.01, 8.17] |
| 5.2.3 Loss of consciousness | 1 | 221 | Risk Ratio(IV, Random, 95% CI) | 0.33[0.01, 8.02] |
| 5.2.4 Psychosis | 4 | 712 | Risk Ratio(IV, Random, 95% CI) | 1.78[0.19, 16.96] |
| 5.2.5 Syncope | 3 | 741 | Risk Ratio(IV, Random, 95% CI) | 1.39[0.23, 8.47] |
| 5.3 Digestive system: gastrointestinal disorders | 1 | | Risk Ratio(IV, Random, 95% CI) | Subtotals only |
| 5.4 Urinary system: kidney infection | 1 | | Risk Ratio(IV, Random, 95% CI) | Subtotals only |
| 5.5 Circulatory and respiratory systems: asthma | 1 | | Risk Ratio(IV, Random, 95% CI) | Subtotals only |
| 5.6 Immune system: cyst rupture | 1 | | Risk Ratio(IV, Random, 95% CI) | Subtotals only |
| 5.7 Other: drug toxicity | 1 | 303 | Risk Ratio(IV, Random, 95% CI) | 0.34[0.01, 8.17] |

### 6 Number of serious adverse events: cross-over trials (endpoint data)

| Outcome or Subgroup | Studies | Participants | Statistical Method | Effect Estimate |
|---|---|---|---|---|
| 6.1 Number of serious adverse events (SAE) | 8 | 1721 | Risk Ratio(IV, Random, 95% CI) | 1.62[0.34, 7.71] |
| 6.2 Hallucinations/psychosis | 4 | 187 | Risk Ratio(IV, Random, 95% CI) | 1.10[0.18, 6.72] |

### 7 Number of non-serious adverse events: parallel-group trials and first-period cross-over trials

| Outcome or Subgroup | Studies | Participants | Statistical Method | Effect Estimate |
|---|---|---|---|---|
| 7.1 Total number of non-serious adverse events | 21 | 3132 | Risk Ratio(IV, Random, 95% CI) | 1.29[1.10, 1.51] |
| 7.2 Subgroup analysis: total number of non-serious adverse events according to dose | 21 | 3135 | Risk Ratio(IV, Random, 95% CI) | 1.28[1.11, 1.49] |
| 7.2.1 Low dose | 2 | 151 | Risk Ratio(IV, Random, 95% CI) | 1.09[0.82, 1.46] |
| 7.2.2 High dose | 10 | 1761 | Risk Ratio(IV, Random, 95% CI) | 1.22[1.10, 1.35] |
| 7.2.3 Unknown dose | 10 | 1223 | Risk Ratio(IV, Random, 95% CI) | 1.37[1.01, 1.87] |

| | | | | |
|---|---|---|---|---|
| 7.3 Nervous system | 21 | | Risk Ratio(IV, Random, 95% CI) | Subtotals only |
| 7.3.1 Affective | 4 | 390 | Risk Ratio(IV, Random, 95% CI) | 2.39[0.48, 11.96] |
| 7.3.2 Aggression | 2 | 417 | Risk Ratio(IV, Random, 95% CI) | 1.16[0.17, 7.80] |
| 7.3.3 Apathy | 1 | 59 | Risk Ratio(IV, Random, 95% CI) | 0.80[0.19, 3.33] |
| 7.3.4 Confusion | 2 | 548 | Risk Ratio(IV, Random, 95% CI) | 1.01[0.22, 4.73] |
| 7.3.5 Depression | 1 | 59 | Risk Ratio(IV, Random, 95% CI) | 0.83[0.22, 3.10] |
| 7.3.6 Dizziness | 3 | 683 | Risk Ratio(IV, Random, 95% CI) | 2.50[0.70, 8.99] |
| 7.3.7 Drowsiness | 4 | 811 | Risk Ratio(IV, Random, 95% CI) | 1.27[0.82, 1.98] |
| 7.3.8 Emotional lability | 1 | 132 | Risk Ratio(IV, Random, 95% CI) | 2.41[0.27, 21.32] |
| 7.3.9 Fatigue | 7 | 858 | Risk Ratio(IV, Random, 95% CI) | 0.76[0.36, 1.63] |
| 7.3.10 Headache | 17 | 2724 | Risk Ratio(IV, Random, 95% CI) | 1.22[0.90, 1.64] |
| 7.3.11 Insomnia | 3 | 349 | Risk Ratio(IV, Random, 95% CI) | 1.31[0.35, 4.93] |
| 7.3.12 Irritability | 11 | 1721 | Risk Ratio(IV, Random, 95% CI) | 1.11[0.77, 1.60] |
| 7.3.13 Nervousness | 2 | 362 | Risk Ratio(IV, Random, 95% CI) | 2.52[0.82, 7.76] |
| 7.3.14 Pain | 1 | 132 | Risk Ratio(IV, Random, 95% CI) | 1.91[0.21, 17.60] |
| 7.3.15 Picking at skin or fingers, nail biting, lip or cheek chewing | 1 | 316 | Risk Ratio(IV, Random, 95% CI) | 1.01[0.60, 1.70] |
| 7.3.16 Sad, tearful or depressed | 4 | 707 | Risk Ratio(IV, Random, 95% CI) | 1.41[0.86, 2.29] |
| 7.3.17 Somnolence | 2 | 173 | Risk Ratio(IV, Random, 95% CI) | 0.59[0.11, 3.11] |
| 7.3.18 Trouble sleeping or sleep problems | 13 | 2416 | Risk Ratio(IV, Random, 95% CI) | 1.60[1.15, 2.23] |
| 7.3.19 Tics or nervous movements | 8 | 1231 | Risk Ratio(IV, Random, 95% CI) | 0.85[0.26, 2.79] |
| 7.3.20 Worried or anxious | 3 | 596 | Risk Ratio(IV, Random, 95% CI) | 1.37[0.84, 2.25] |
| 7.4 Digestive system | 18 | | Risk Ratio(IV, Random, 95% CI) | Subtotals only |
| 7.4.1 Decreased appetite | 16 | 2962 | Risk Ratio(IV, Random, 95% CI) | 3.66[2.56, 5.23] |
| 7.4.2 Decreased weight | 6 | 859 | Risk Ratio(IV, Random, 95% CI) | 3.89[1.43, 10.59] |
| 7.4.3 Diarrhoea | 5 | 857 | Risk Ratio(IV, Random, 95% CI) | 1.07[0.41, 2.74] |
| 7.4.4 Dyspepsia | 2 | 159 | Risk Ratio(IV, Random, 95% CI) | 1.80[0.71, 4.54] |
| 7.4.5 Increased appetite | 1 | 179 | Risk Ratio(IV, Random, 95% CI) | 0.07[0.00, 1.43] |
| 7.4.6 Nausea | 11 | 1995 | Risk Ratio(IV, Random, 95% CI) | 1.30[0.85, 1.99] |
| 7.4.7 Stomachache | 13 | 2341 | Risk Ratio(IV, Random, 95% CI) | 1.30[1.00, 1.69] |
| 7.4.8 Vomiting | 11 | 1916 | Risk Ratio(IV, Random, 95% CI) | 1.17[0.76, 1.79] |
| 7.5 Circulatory and respiratory systems | 8 | | Risk Ratio(IV, Random, 95% CI) | Subtotals only |
| 7.5.1 ECG: prolonged QT-interval | 2 | 466 | Risk Ratio(IV, Random, 95% CI) | 0.81[0.13, 5.00] |
| 7.5.2 ECG: tachycardia | 1 | 245 | Risk Ratio(IV, Random, 95% CI) | 1.04[0.11, 10.18] |
| 7.5.3 Cough | 4 | 996 | Risk Ratio(IV, Random, 95% CI) | 0.95[0.41, 2.18] |
| 7.5.4 Nasal congestion | 2 | 479 | Risk Ratio(IV, Random, 95% CI) | 1.19[0.59, 2.41] |
| 7.5.5 Pharyngolaryngeal pain | 1 | 303 | Risk Ratio(IV, Random, 95% CI) | 1.12[0.59, 2.13] |
| 7.5.6 Supraventricular extrasystoles | 1 | 17 | Risk Ratio(IV, Random, 95% CI) | 3.00[0.11, 84.55] |
| 7.5.7 Upper respiratory tract infection | 1 | 217 | Risk Ratio(IV, Random, 95% CI) | 1.07[0.42, 2.76] |
| 7.6 Skeletal and muscular systems | 2 | | Risk Ratio(IV, Random, 95% CI) | Subtotals only |
| 7.6.1 Arthralgia | 1 | 303 | Risk Ratio(IV, Random, 95% CI) | 0.67[0.24, 1.84] |
| 7.6.2 Asthenia | 1 | 177 | Risk Ratio(IV, Random, 95% CI) | 0.21[0.01, 4.25] |
| 7.6.3 Back pain | 1 | 303 | Risk Ratio(IV, Random, 95% CI) | 0.81[0.39, 1.66] |
| 7.6.4 Myalgia | 1 | 303 | Risk Ratio(IV, Random, 95% CI) | 0.60[0.23, 1.62] |
| 7.6.5 Toothache | 1 | 303 | Risk Ratio(IV, Random, 95% CI) | 1.01[0.43, 2.35] |

| | | | | |
|---|---|---|---|---|
| 7.7 Immune system | 7 | | Risk Ratio(IV, Random, 95% CI) | Subtotals only |
| 7.7.1 Gastroenteritis | 3 | 435 | Risk Ratio(IV, Random, 95% CI) | 4.63[0.99, 21.72] |
| 7.7.2 Influenza | 3 | 624 | Risk Ratio(IV, Random, 95% CI) | 0.65[0.20, 2.10] |
| 7.7.3 Nasopharyngitis | 5 | 979 | Risk Ratio(IV, Random, 95% CI) | 1.15[0.70, 1.87] |
| 7.7.4 Otitis media | 1 | 100 | Risk Ratio(IV, Random, 95% CI) | 1.77[0.17, 18.94] |
| 7.7.5 Pharyngitis | 2 | 293 | Risk Ratio(IV, Random, 95% CI) | 2.43[0.49, 12.05] |
| 7.7.6 Pyrexia | 2 | 400 | Risk Ratio(IV, Random, 95% CI) | 1.02[0.01, 87.72] |
| 7.7.7 Rhinitis | 1 | 132 | Risk Ratio(IV, Random, 95% CI) | 1.28[0.43, 3.79] |
| 7.7.8 Upper respiratory tract infection - not otherwise specified (NOS) | 5 | 917 | Risk Ratio(IV, Random, 95% CI) | 1.19[0.68, 2.06] |
| 7.7.9 Viral infection NOS | 3 | 614 | Risk Ratio(IV, Random, 95% CI) | 0.70[0.23, 2.15] |
| 7.8 Height | 1 | | Mean Difference(IV, Random, 95% CI) | No totals |
| 7.9 Weight | 5 | 805 | Std. Mean Difference(IV, Random, 95% CI) | -1.12[-1.55, -0.70] |
| 7.10 BMI | 1 | | Mean Difference(IV, Random, 95% CI) | No totals |
| 7.11 Vital signs | 9 | 3374 | Mean Difference(IV, Random, 95% CI) | 1.41[0.30, 2.52] |
| 7.11.1 Diastolic blood pressure (mmHg) | 8 | 1067 | Mean Difference(IV, Random, 95% CI) | 0.94[-0.12, 2.01] |
| 7.11.2 Systolic blood pressure (mmHg) | 8 | 1067 | Mean Difference(IV, Random, 95% CI) | -0.05[-1.25, 1.16] |
| 7.11.3 Pulse or heart rate (bpm) | 8 | 1240 | Mean Difference(IV, Random, 95% CI) | 3.41[0.87, 5.94] |
| 7.12 Other | 5 | 1815 | Risk Ratio(IV, Random, 95% CI) | 1.20[0.56, 2.57] |
| 7.12.1 Accidental injury | 3 | 656 | Risk Ratio(IV, Random, 95% CI) | 0.99[0.48, 2.07] |
| 7.12.2 Epistasis | 1 | 132 | Risk Ratio(IV, Random, 95% CI) | 4.25[0.23, 77.22] |
| 7.12.3 Excoriation | 1 | 303 | Risk Ratio(IV, Random, 95% CI) | 3.52[1.19, 10.46] |
| 7.12.4 Overdose | 1 | 221 | Risk Ratio(IV, Random, 95% CI) | 2.97[0.12, 72.20] |
| 7.12.5 Skin disorder (rash) | 2 | 200 | Risk Ratio(IV, Random, 95% CI) | 0.52[0.01, 26.44] |
| 7.12.6 Skin laceration | 1 | 303 | Risk Ratio(IV, Random, 95% CI) | 0.42[0.15, 1.16] |

## 8 Number of non-serious adverse events: cross-over trials (endpoint data)

| Outcome or Subgroup | Studies | Participants | Statistical Method | Effect Estimate |
|---|---|---|---|---|
| 8.1 Total number of non-serious adverse events | 21 | 2072 | Risk Ratio(IV, Random, 95% CI) | 1.33[1.11, 1.58] |
| 8.2 Subgroup analysis: total number of non-serious adverse events according to dose | 21 | 2859 | Risk Ratio(IV, Random, 95% CI) | 1.26[1.11, 1.44] |
| 8.2.1 Low dose | 16 | 1539 | Risk Ratio(IV, Random, 95% CI) | 1.11[0.94, 1.31] |
| 8.2.2 High dose | 12 | 1080 | Risk Ratio(IV, Random, 95% CI) | 1.57[1.22, 2.01] |
| 8.2.3 Unknown dose | 2 | 240 | Risk Ratio(IV, Random, 95% CI) | 0.98[0.51, 1.86] |

| | | | | |
|---|---|---|---|---|
| 8.3 Nervous system | 50 | | Risk Ratio(IV, Random, 95% CI) | Subtotals only |
| 8.3.1 Aggression | 2 | 589 | Risk Ratio(IV, Random, 95% CI) | 0.52[0.17, 1.60] |
| 8.3.2 Agitation | 1 | 62 | Risk Ratio(IV, Random, 95% CI) | 1.18[0.38, 3.60] |
| 8.3.3 Anger | 3 | 264 | Risk Ratio(IV, Random, 95% CI) | 0.45[0.26, 0.77] |
| 8.3.4 Behavioural complaints | 1 | 82 | Risk Ratio(IV, Random, 95% CI) | 0.55[0.35, 0.86] |
| 8.3.5 Buccal or lingual movements | 4 | 302 | Risk Ratio(IV, Random, 95% CI) | 1.06[0.62, 1.79] |
| 8.3.6 Compulsive acts | 1 | 90 | Risk Ratio(IV, Random, 95% CI) | 2.57[1.45, 4.56] |
| 8.3.7 Daydreaming | 3 | 222 | Risk Ratio(IV, Random, 95% CI) | 0.66[0.44, 0.98] |
| 8.3.8 Dizziness | 9 | 746 | Risk Ratio(IV, Random, 95% CI) | 1.17[0.89, 1.55] |
| 8.3.9 Drowsiness: dull, tired, listless or sleepy | 21 | 1350 | Risk Ratio(IV, Random, 95% CI) | 0.97[0.73, 1.28] |
| 8.3.10 Euphoria | 6 | 405 | Risk Ratio(IV, Random, 95% CI) | 1.06[0.72, 1.57] |
| 8.3.11 Headache | 37 | 3752 | Risk Ratio(IV, Random, 95% CI) | 1.21[1.01, 1.45] |
| 8.3.12 Insomnia or sleep problems | 31 | 3270 | Risk Ratio(IV, Random, 95% CI) | 1.57[1.20, 2.06] |
| 8.3.13 Irritability | 23 | 2238 | Risk Ratio(IV, Random, 95% CI) | 0.92[0.66, 1.27] |
| 8.3.14 Nightmares | 10 | 686 | Risk Ratio(IV, Random, 95% CI) | 0.97[0.66, 1.42] |
| 8.3.15 Overly meticulous | 1 | 96 | Risk Ratio(IV, Random, 95% CI) | 40.77[2.35, 706.72] |
| 8.3.16 Obsessive thinking | 1 | 90 | Risk Ratio(IV, Random, 95% CI) | 2.35[1.53, 3.62] |
| 8.3.17 Picking at skin or fingers, nail biting, lip or cheek chewing | 15 | 888 | Risk Ratio(IV, Random, 95% CI) | 1.12[0.88, 1.41] |
| 8.3.18 Repetitive language | 1 | 48 | Risk Ratio(IV, Random, 95% CI) | 1.00[0.32, 3.10] |
| 8.3.19 Sad, tearful or depressed | 23 | 1849 | Risk Ratio(IV, Random, 95% CI) | 1.15[0.94, 1.41] |
| 8.3.20 Socially withdrawn - decreased interaction with others | 12 | 771 | Risk Ratio(IV, Random, 95% CI) | 1.24[0.82, 1.87] |
| 8.3.21 Sleep efficiency (SEF) | 2 | 108 | Risk Ratio(IV, Random, 95% CI) | 0.48[0.02, 14.28] |
| 8.3.22 Stares a lot | 9 | 904 | Risk Ratio(IV, Random, 95% CI) | 1.03[0.75, 1.40] |
| 8.3.23 Tics or nervous movements | 19 | 1403 | Risk Ratio(IV, Random, 95% CI) | 1.33[1.03, 1.72] |
| 8.3.24 Unusual blinking | 1 | 48 | Risk Ratio(IV, Random, 95% CI) | 3.13[0.12, 80.68] |
| 8.3.25 Worried or anxious | 20 | 1673 | Risk Ratio(IV, Random, 95% CI) | 0.82[0.60, 1.12] |
| 8.4 Digestive system | 42 | | Risk Ratio(IV, Random, 95% CI) | Subtotals only |
| 8.4.1 Decreased appetite or loss of appetite | 35 | 3862 | Risk Ratio(IV, Random, 95% CI) | 3.04[2.35, 3.94] |
| 8.4.2 Diarrhoea | 3 | 402 | Risk Ratio(IV, Random, 95% CI) | 0.58[0.19, 1.74] |
| 8.4.3 Dry mouth | 5 | 342 | Risk Ratio(IV, Random, 95% CI) | 1.25[0.54, 2.90] |
| 8.4.4 Dyspepsia | 1 | 62 | Risk Ratio(IV, Random, 95% CI) | 0.22[0.02, 2.14] |
| 8.4.5 Nausea | 9 | 768 | Risk Ratio(IV, Random, 95% CI) | 1.52[1.00, 2.30] |
| 8.4.6 Increased appetite | 1 | 136 | Risk Ratio(IV, Random, 95% CI) | 0.20[0.08, 0.50] |
| 8.4.7 Stomachache | 33 | 3777 | Risk Ratio(IV, Random, 95% CI) | 1.61[1.27, 2.04] |
| 8.4.8 Vomiting | 4 | 710 | Risk Ratio(IV, Random, 95% CI) | 0.90[0.26, 3.11] |
| 8.5 Urinary system: urinary incontinence | 1 | | Risk Ratio(IV, Random, 95% CI) | No totals |
| 8.6 Skeletal and muscular system: somatic complaints | 1 | | Mean Difference(IV, Random, 95% CI) | No totals |
| 8.7 Immune system | 7 | | Risk Ratio(IV, Random, 95% CI) | Subtotals only |
| 8.7.1 Allergic rhinitis | 4 | 475 | Risk Ratio(IV, Random, 95% CI) | 1.38[0.35, 5.51] |
| 8.7.2 Fever | 2 | 91 | Risk Ratio(IV, Random, 95% CI) | 1.39[0.09, 20.56] |
| 8.7.3 Lymphadenitis | 2 | 296 | Risk Ratio(IV, Random, 95% CI) | 3.93[0.44, 35.11] |
| 8.7.4 Pharyngolaryngeal pain | 1 | 160 | Risk Ratio(IV, Random, 95% CI) | 2.00[0.19, 21.62] |
| 8.7.5 Pharyngitis | 4 | 754 | Risk Ratio(IV, Random, 95% CI) | 0.71[0.19, 2.62] |
| 8.7.6 Upper respiratory tract infection | 5 | 888 | Risk Ratio(IV, Random, 95% CI) | 0.61[0.27, 1.37] |
| 8.8 Skin | 3 | | Risk Ratio(IV, Random, 95% CI) | Subtotals only |
| 8.8.1 Rash | 2 | 208 | Risk Ratio(IV, Random, 95% CI) | 0.96[0.14, 6.41] |
| 8.8.2 Skin laceration | 1 | 167 | Risk Ratio(IV, Random, 95% CI) | 2.96[0.12, 71.75] |

| | | | | |
|---|---|---|---|---|
| 8.9 Vital signs | 14 | | Mean Difference(IV, Random, 95% CI) | Subtotals only |
| 8.9.1 Diastolic blood pressure (mmHg) | 11 | 755 | Mean Difference(IV, Random, 95% CI) | 1.23[-0.39, 2.86] |
| 8.9.2 Systolic blood pressure (mmHg) | 11 | 755 | Mean Difference(IV, Random, 95% CI) | 0.53[-1.30, 2.36] |
| 8.9.3 Pulse or heart rate (bpm) | 14 | 939 | Mean Difference(IV, Random, 95% CI) | 5.06[2.88, 7.24] |
| 8.10 Height (cm) | 1 | | Mean Difference(IV, Random, 95% CI) | No totals |
| 8.11 Weight | 6 | 530 | Std. Mean Difference(IV, Random, 95% CI) | -0.06[-0.23, 0.11] |

## 9 Teacher-rated general behaviour

| Outcome or Subgroup | Studies | Participants | Statistical Method | Effect Estimate |
|---|---|---|---|---|
| 9.1 All parallel-group trials and first-period cross-over trials: risk of bias | 5 | 668 | Std. Mean Difference(IV, Random, 95% CI) | -0.87[-1.04, -0.71] |
| 9.1.1 Low risk of bias | 0 | 0 | Std. Mean Difference(IV, Random, 95% CI) | Not estimable |
| 9.1.2 High risk of bias | 5 | 668 | Std. Mean Difference(IV, Random, 95% CI) | -0.87[-1.04, -0.71] |
| 9.2 Subgroup analysis: types of scales | 5 | 668 | Std. Mean Difference(IV, Random, 95% CI) | -0.87[-1.04, -0.71] |
| 9.2.1 Conners' Global Index - Teacher (CGI-T) | 1 | 314 | Std. Mean Difference(IV, Random, 95% CI) | -0.91[-1.14, -0.68] |
| 9.2.2 Groninger Behaviour Observation Scale (GBOS) | 1 | 43 | Std. Mean Difference(IV, Random, 95% CI) | -0.84[-1.46, -0.21] |
| 9.2.3 Conners' Teacher Rating Scale - Conduct problems | 1 | 25 | Std. Mean Difference(IV, Random, 95% CI) | -0.67[-1.48, 0.14] |
| 9.2.4 IOWA Conners' Rating Scale - Oppositional/Defiant (IOWA-O/D) | 2 | 286 | Std. Mean Difference(IV, Random, 95% CI) | -0.86[-1.12, -0.59] |
| 9.3 Subgroup analysis: dose | 5 | 696 | Std. Mean Difference(IV, Random, 95% CI) | -0.85[-1.02, -0.69] |
| 9.3.1 Low dose | 2 | 71 | Std. Mean Difference(IV, Random, 95% CI) | -0.67[-1.16, -0.19] |
| 9.3.2 High dose | 3 | 466 | Std. Mean Difference(IV, Random, 95% CI) | -0.89[-1.08, -0.70] |
| 9.3.3 Unknown dose | 1 | 159 | Std. Mean Difference(IV, Random, 95% CI) | -0.84[-1.21, -0.46] |
| 9.4 Subgroup analysis: duration of treatment | 5 | 668 | Std. Mean Difference(IV, Random, 95% CI) | -0.87[-1.04, -0.71] |
| 9.4.1 Short term (up to 6 months) | 5 | 668 | Std. Mean Difference(IV, Random, 95% CI) | -0.87[-1.04, -0.71] |
| 9.4.2 Long term (over 6 months) | 0 | 0 | Std. Mean Difference(IV, Random, 95% CI) | Not estimable |
| 9.5 Subgroup analysis: parallel-group trials versus first-period cross-over trials | 5 | 668 | Std. Mean Difference(IV, Random, 95% CI) | -0.87[-1.04, -0.71] |
| 9.5.1 Parallel-group trials | 5 | 668 | Std. Mean Difference(IV, Random, 95% CI) | -0.87[-1.04, -0.71] |
| 9.5.2 First-period cross-over trials | 0 | 0 | Std. Mean Difference(IV, Random, 95% CI) | Not estimable |
| 9.6 General behaviour, cross-over trials (endpoint data) | 16 | 2014 | Std. Mean Difference(IV, Random, 95% CI) | -0.69[-0.78, -0.60] |
| 9.6.1 Low dose | 13 | 1110 | Std. Mean Difference(IV, Random, 95% CI) | -0.60[-0.72, -0.48] |
| 9.6.2 High dose | 12 | 904 | Std. Mean Difference(IV, Random, 95% CI) | -0.82[-0.95, -0.68] |

| | | | | |
|---|---|---|---|---|
| 9.7 Subgroup analysis: general behaviour, cross-over trials (endpoint data): risk of bias | 16 | 1308 | Std. Mean Difference(IV, Random, 95% CI) | -0.75[-0.87, -0.63] |
| 9.7.1 Low risk of bias | 0 | 0 | Std. Mean Difference(IV, Random, 95% CI) | Not estimable |
| 9.7.2 High risk of bias | 16 | 1308 | Std. Mean Difference(IV, Random, 95% CI) | -0.75[-0.87, -0.63] |
| 9.8 Subgroup analysis: all parallel-group trials and first-period cross-over trials (teacher-rated) versus cross-over trials (endpoint data) | 21 | 1976 | Std. Mean Difference(IV, Random, 95% CI) | -0.79[-0.88, -0.70] |
| 9.8.1 All parallel-group trials and first-period cross-over trials | 5 | 668 | Std. Mean Difference(IV, Random, 95% CI) | -0.87[-1.04, -0.71] |
| 9.8.2 Cross-over trials (endpoint data) | 16 | 1308 | Std. Mean Difference(IV, Random, 95% CI) | -0.75[-0.87, -0.63] |

## 10 Independent assessor-rated general behaviour

| Outcome or Subgroup | Studies | Participants | Statistical Method | Effect Estimate |
|---|---|---|---|---|
| 10.1 General behaviour, cross-over trials (endpoint data) | 8 | 1241 | Std. Mean Difference(IV, Random, 95% CI) | -0.60[-0.75, -0.46] |
| 10.1.1 Low dose | 7 | 903 | Std. Mean Difference(IV, Random, 95% CI) | -0.56[-0.76, -0.36] |
| 10.1.2 High dose | 5 | 338 | Std. Mean Difference(IV, Random, 95% CI) | -0.71[-0.93, -0.49] |
| 10.2 Subgroup analysis: general behaviour, cross-over trials (endpoint data): risk of bias | 8 | 951 | Std. Mean Difference(IV, Random, 95% CI) | -0.69[-0.88, -0.49] |
| 10.2.1 Low risk of bias | 0 | 0 | Std. Mean Difference(IV, Random, 95% CI) | Not estimable |
| 10.2.2 High risk of bias | 8 | 951 | Std. Mean Difference(IV, Random, 95% CI) | -0.69[-0.88, -0.49] |
| 10.3 Subgroup analysis: all parallel-group trials and first-period cross-over trials (independent assessor-rated) compared with cross-over trials (endpoint data) | 8 | 951 | Std. Mean Difference(IV, Random, 95% CI) | -0.69[-0.88, -0.49] |
| 10.3.1 Parallel-group trials and first-period cross-over trials | 0 | 0 | Std. Mean Difference(IV, Random, 95% CI) | Not estimable |
| 10.3.2 Cross-over trials (endpoint data) | 8 | 951 | Std. Mean Difference(IV, Random, 95% CI) | -0.69[-0.88, -0.49] |

## 11 Parent-rated general behaviour

| Outcome or Subgroup | Studies | Participants | Statistical Method | Effect Estimate |
|---|---|---|---|---|
| 11.1 All parallel-group trials and first-period cross-over trials | 6 | 670 | Std. Mean Difference(IV, Random, 95% CI) | -0.53[-0.78, -0.27] |
| 11.2 Subgroup analysis: risk of bias | 6 | 670 | Std. Mean Difference(IV, Random, 95% CI) | -0.53[-0.78, -0.27] |
| 11.2.1 Low risk of bias | 0 | 0 | Std. Mean Difference(IV, Random, 95% CI) | Not estimable |
| 11.2.2 High risk of bias | 6 | 670 | Std. Mean Difference(IV, Random, 95% CI) | -0.53[-0.78, -0.27] |

| | | | | |
|---|---|---|---|---|
| 11.3 Subgroup analysis: types of scales | 6 | 670 | Std. Mean Difference(IV, Random, 95% CI) | -0.53[-0.78, -0.27] |
| 11.3.1 The Weekly Parent Ratings of Evening and Morning Behaviour (WPREMB) - Revised | 1 | 17 | Std. Mean Difference(IV, Random, 95% CI) | 0.50[-0.47, 1.47] |
| 11.3.2 Conners' Global Index (CGI) - Parent | 2 | 352 | Std. Mean Difference(IV, Random, 95% CI) | -0.41[-0.63, -0.20] |
| 11.3.3 Swanson, Nolan and Pelham, Fourth Edition - Oppositional (SNAP-IV-Oppositional) | 1 | 15 | Std. Mean Difference(IV, Random, 95% CI) | -0.86[-1.95, 0.23] |
| 11.3.4 IOWA Conners' Rating Scale - Oppositional/Defiant (IOWA-I/O) | 2 | 286 | Std. Mean Difference(IV, Random, 95% CI) | -0.75[-1.01, -0.49] |
| 11.4 Subgroup analysis: parallel-group trials compared with first-period cross-over trials | 6 | 670 | Std. Mean Difference(IV, Random, 95% CI) | -0.53[-0.78, -0.27] |
| 11.4.1 Parallel-group trials | 5 | 655 | Std. Mean Difference(IV, Random, 95% CI) | -0.51[-0.78, -0.23] |
| 11.4.2 First-period cross-over trials | 1 | 15 | Std. Mean Difference(IV, Random, 95% CI) | -0.86[-1.95, 0.23] |
| 11.5 Subgroup analysis: duration of treatment | 6 | 670 | Std. Mean Difference(IV, Random, 95% CI) | -0.53[-0.78, -0.27] |
| 11.5.1 Short term (up to 6 months) | 6 | 670 | Std. Mean Difference(IV, Random, 95% CI) | -0.53[-0.78, -0.27] |
| 11.5.2 Long term (over 6 months) | 0 | 0 | Std. Mean Difference(IV, Random, 95% CI) | Not estimable |
| 11.6 Subgroup analysis: dose | 6 | 670 | Std. Mean Difference(IV, Random, 95% CI) | -0.53[-0.78, -0.27] |
| 11.6.1 Low dose | 0 | 0 | Std. Mean Difference(IV, Random, 95% CI) | Not estimable |
| 11.6.2 High dose | 4 | 496 | Std. Mean Difference(IV, Random, 95% CI) | -0.42[-0.77, -0.08] |
| 11.6.3 Unknown dose | 2 | 174 | Std. Mean Difference(IV, Random, 95% CI) | -0.73[-1.08, -0.38] |
| 11.7 General behaviour, cross-over trials (endpoint data) | 6 | 550 | Std. Mean Difference(IV, Random, 95% CI) | -0.75[-0.93, -0.56] |
| 11.7.1 Low dose | 5 | 248 | Std. Mean Difference(IV, Random, 95% CI) | -0.65[-0.93, -0.38] |
| 11.7.2 High dose | 4 | 302 | Std. Mean Difference(IV, Random, 95% CI) | -0.83[-1.07, -0.60] |
| 11.8 Subgroup analysis: general behaviour, cross-over trials (endpoint data): risk of bias | 6 | 384 | Std. Mean Difference(IV, Random, 95% CI) | -0.84[-1.05, -0.63] |
| 11.8.1 Low risk of bias | 0 | 0 | Std. Mean Difference(IV, Random, 95% CI) | Not estimable |
| 11.8.2 High risk of bias | 6 | 384 | Std. Mean Difference(IV, Random, 95% CI) | -0.84[-1.05, -0.63] |
| 11.9 Subgroup analysis: all parallel-group trials and first-period cross-over trials (parent-rated) compared with cross-over trials (endpoint data) | 12 | 1054 | Std. Mean Difference(IV, Random, 95% CI) | -0.68[-0.86, -0.50] |
| 11.9.1 All parallel-group trials and first-period cross-over trials | 6 | 670 | Std. Mean Difference(IV, Random, 95% CI) | -0.53[-0.78, -0.27] |
| 11.9.2 Cross-over trials (endpoint data) | 6 | 384 | Std. Mean Difference(IV, Random, 95% CI) | -0.84[-1.05, -0.63] |

## 12 Additional subgroup analyses of general behaviour: parallel-group trials and first-period cross-over trials

| Outcome or Subgroup | Studies | Participants | Statistical Method | Effect Estimate |
|---|---|---|---|---|

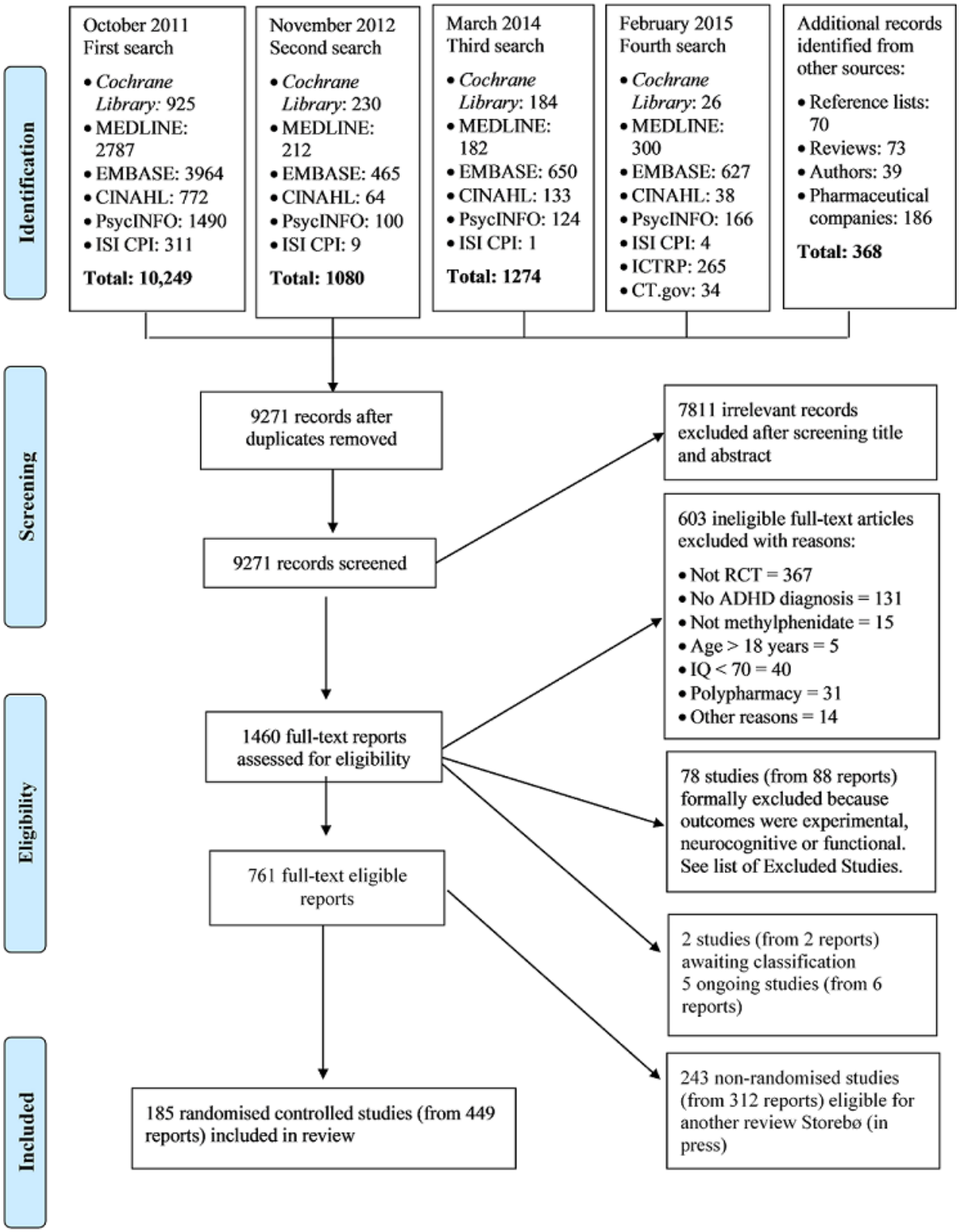
| | | | | |
|---|---|---|---|---|
| 12.1 Comparisions of raters | 8 | 1338 | Std. Mean Difference(IV, Random, 95% CI) | -0.69[-0.86, -0.52] |
| 12.1.1 Teacher-rated | 5 | 668 | Std. Mean Difference(IV, Random, 95% CI) | -0.87[-1.04, -0.71] |
| 12.1.2 Independent assessor-rated | 0 | 0 | Std. Mean Difference(IV, Random, 95% CI) | Not estimable |
| 12.1.3 Parent-rated | 6 | 670 | Std. Mean Difference(IV, Random, 95% CI) | -0.53[-0.78, -0.27] |
| 12.2 Comorbidity versus no comorbidity | 7 | 579 | Std. Mean Difference(IV, Random, 95% CI) | -0.70[-0.98, -0.43] |
| 12.2.1 ADHD with comorbidity | 6 | 265 | Std. Mean Difference(IV, Random, 95% CI) | -0.59[-0.95, -0.23] |
| 12.2.2 ADHD without comorbidity | 1 | 314 | Std. Mean Difference(IV, Random, 95% CI) | -0.91[-1.14, -0.68] |
| 12.3 Cross-over trials: first-period data versus endpoint data (teacher-, parent-, and independent assessor-rated) | 1 | | Mean Difference(IV, Random, 95% CI) | Subtotals only |
| 12.3.1 First-period data | 1 | 16 | Mean Difference(IV, Random, 95% CI) | -0.81[-1.75, 0.13] |
| 12.3.2 Endpoint data | 1 | 14 | Mean Difference(IV, Random, 95% CI) | 0.14[-0.71, 1.00] |

### 13 Quality of life: parallel-group trials and first-period cross-over trials

| Outcome or Subgroup | Studies | Participants | Statistical Method | Effect Estimate |
|---|---|---|---|---|
| 13.1 Subgroup analysis: types of scales | 3 | 514 | Std. Mean Difference(IV, Random, 95% CI) | 0.61[0.42, 0.80] |
| 13.1.1 Child Health Questionnaire (CHQ) | 1 | 257 | Std. Mean Difference(IV, Random, 95% CI) | 0.54[0.25, 0.83] |
| 13.1.2 Children´s Global Assessment Scale (CGAS) | 1 | 36 | Std. Mean Difference(IV, Random, 95% CI) | 0.79[0.10, 1.47] |
| 13.1.3 Child Health and Illness Profile, Child Edition: Parent Report Form (CHIP-CE:PRF) | 1 | 221 | Std. Mean Difference(IV, Random, 95% CI) | 0.64[0.37, 0.91] |

## Figures

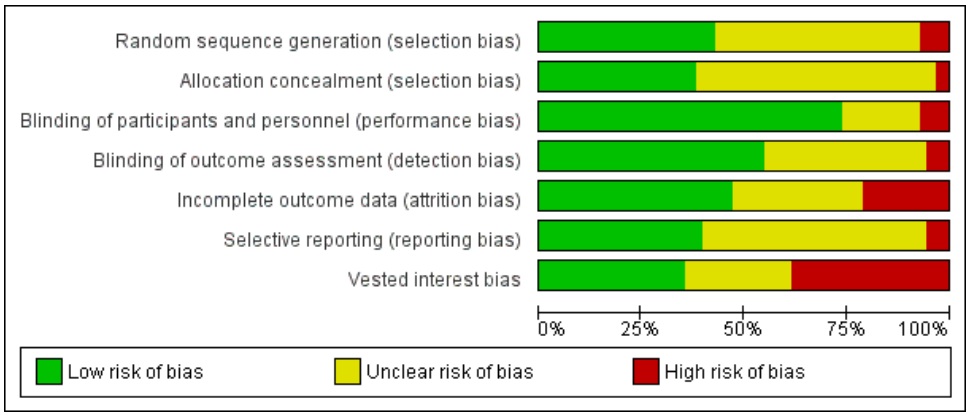
### Figure 1




*Caption*

Flow chart.

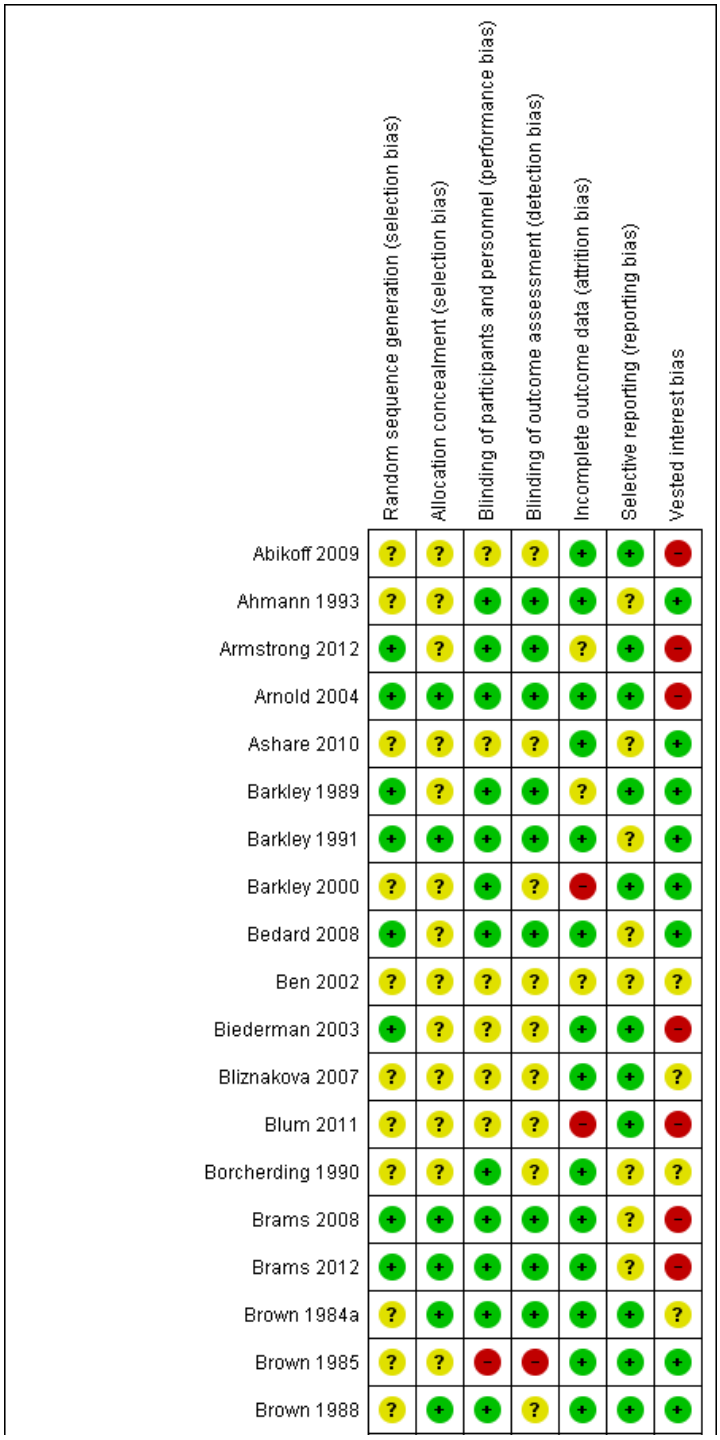
**Figure 2**

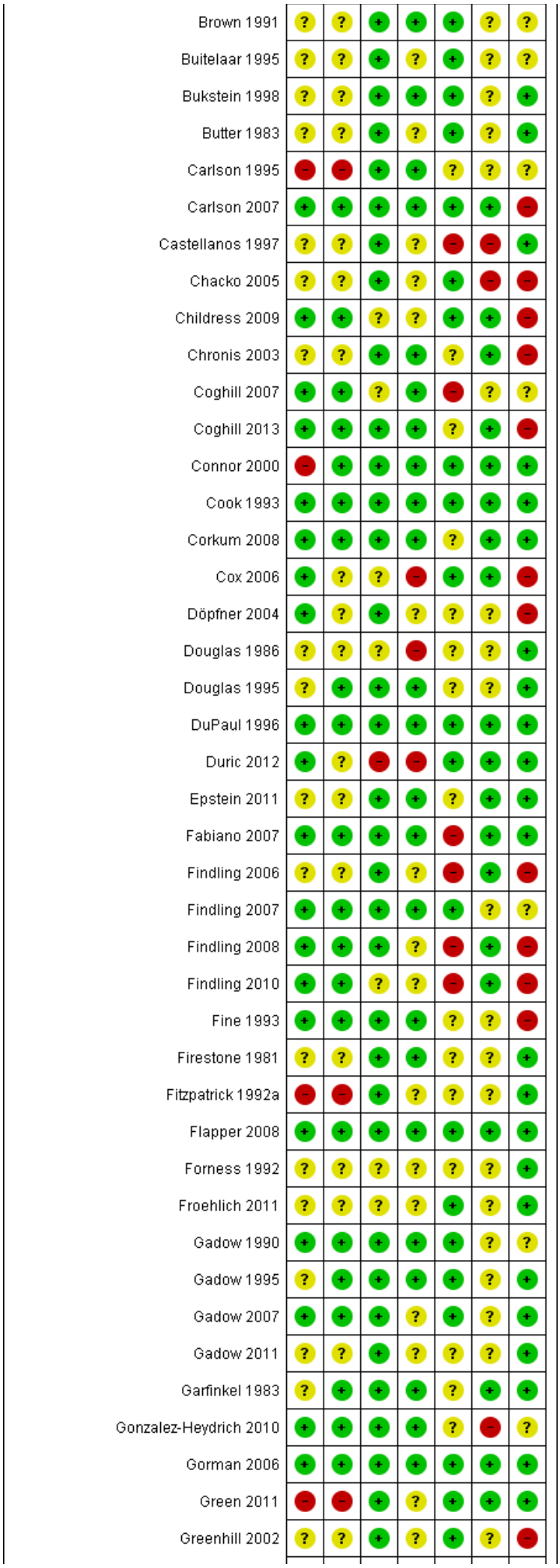


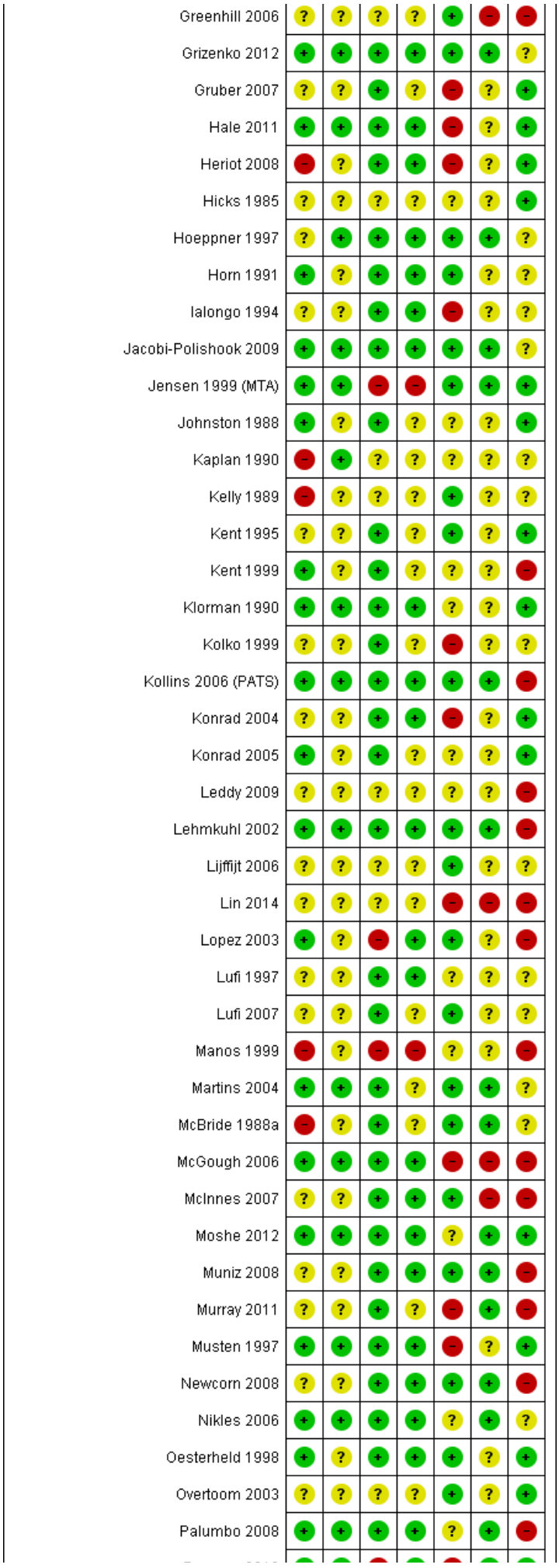

*Caption*

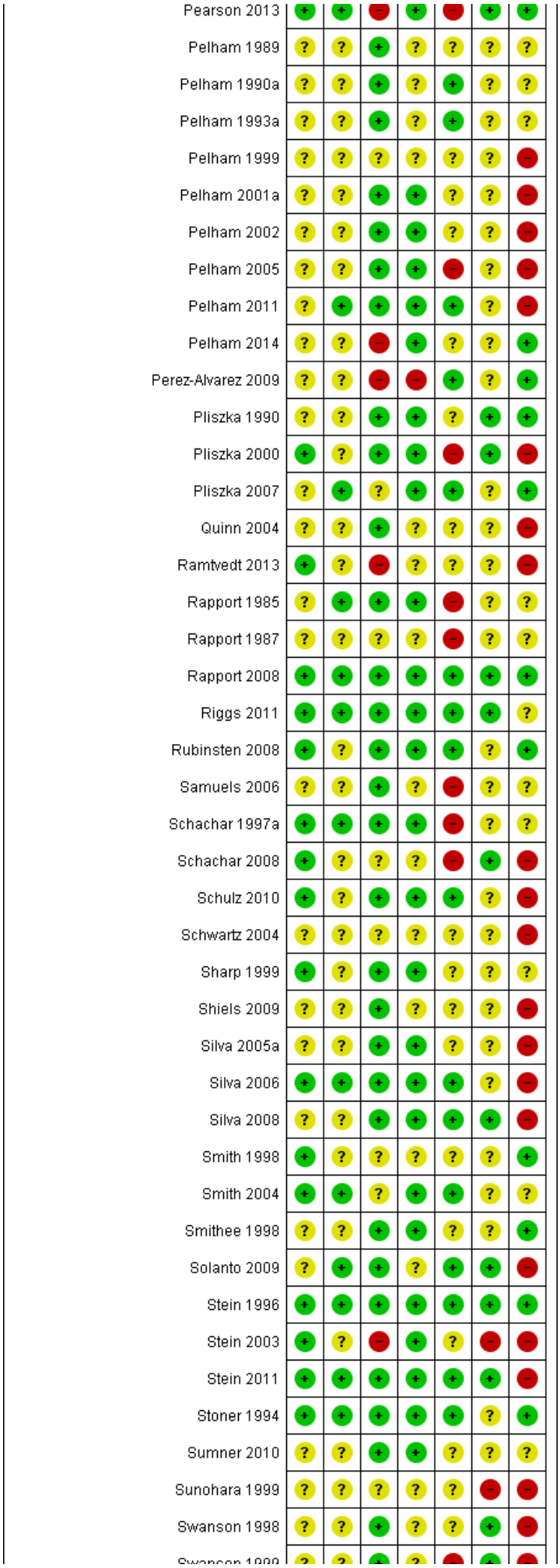
Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

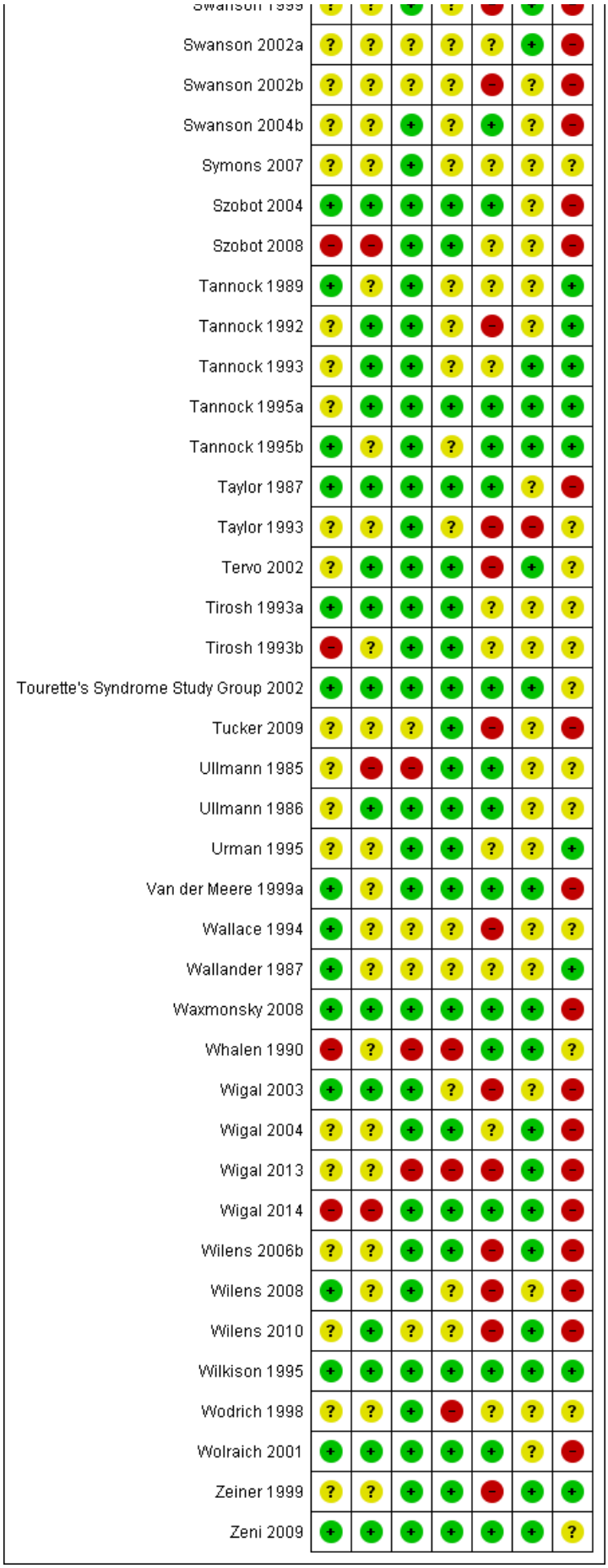
## Figure 3




Brown 1991
Buitelaar 1995
Bukstein 1998
Butter 1983
Carlson 1995
Carlson 2007
Castellanos 1997
Chacko 2005
Childress 2009
Chronis 2003
Coghill 2007
Coghill 2013
Connor 2000
Cook 1993
Corkum 2008
Cox 2006
Döpfner 2004
Douglas 1986
Douglas 1995
DuPaul 1996
Duric 2012
Epstein 2011
Fabiano 2007
Findling 2006
Findling 2007
Findling 2008
Findling 2010
Fine 1993
Firestone 1981
Fitzpatrick 1992a
Flapper 2008
Forness 1992
Froehlich 2011
Gadow 1990
Gadow 1995
Gadow 2007
Gadow 2011
Garfinkel 1983
Gonzalez-Heydrich 2010
Gorman 2006
Green 2011
Greenhill 2002


Greenhill 2006
Grizenko 2012
Gruber 2007
Hale 2011
Heriot 2008
Hicks 1985
Hoeppner 1997
Horn 1991
Ialongo 1994
Jacobi-Polishook 2009
Jensen 1999 (MTA)
Johnston 1988
Kaplan 1990
Kelly 1989
Kent 1995
Kent 1999
Klorman 1990
Kolko 1999
Kollins 2006 (PATS)
Konrad 2004
Konrad 2005
Leddy 2009
Lehmkuhl 2002
Lijffijt 2006
Lin 2014
Lopez 2003
Lufi 1997
Lufi 2007
Manos 1999
Martins 2004
McBride 1988a
McGough 2006
McInnes 2007
Moshe 2012
Muniz 2008
Murray 2011
Musten 1997
Newcorn 2008
Nikles 2006
Oesterheld 1998
Overtoom 2003
Palumbo 2008

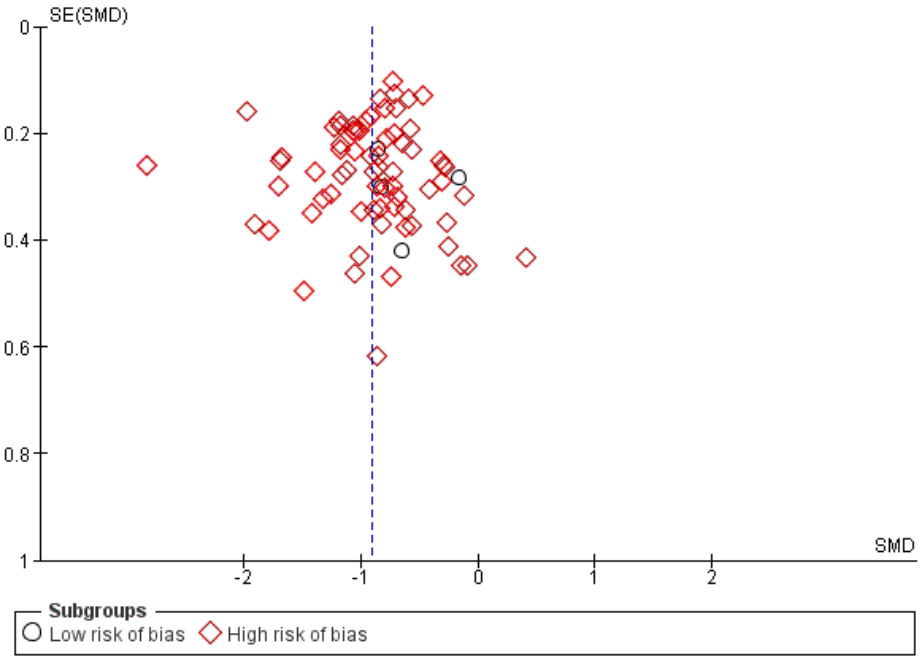

Pearson 2013
Pelham 1989
Pelham 1990a
Pelham 1993a
Pelham 1999
Pelham 2001a
Pelham 2002
Pelham 2005
Pelham 2011
Pelham 2014
Perez-Alvarez 2009
Pliszka 1990
Pliszka 2000
Pliszka 2007
Quinn 2004
Ramtvedt 2013
Rapport 1985
Rapport 1987
Rapport 2008
Riggs 2011
Rubinsten 2008
Samuels 2006
Schachar 1997a
Schachar 2008
Schulz 2010
Schwartz 2004
Sharp 1999
Shiels 2009
Silva 2005a
Silva 2006
Silva 2008
Smith 1998
Smith 2004
Smithee 1998
Solanto 2009
Stein 1996
Stein 2003
Stein 2011
Stoner 1994
Sumner 2010
Sunohara 1999
Swanson 1998




*Caption*

Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.

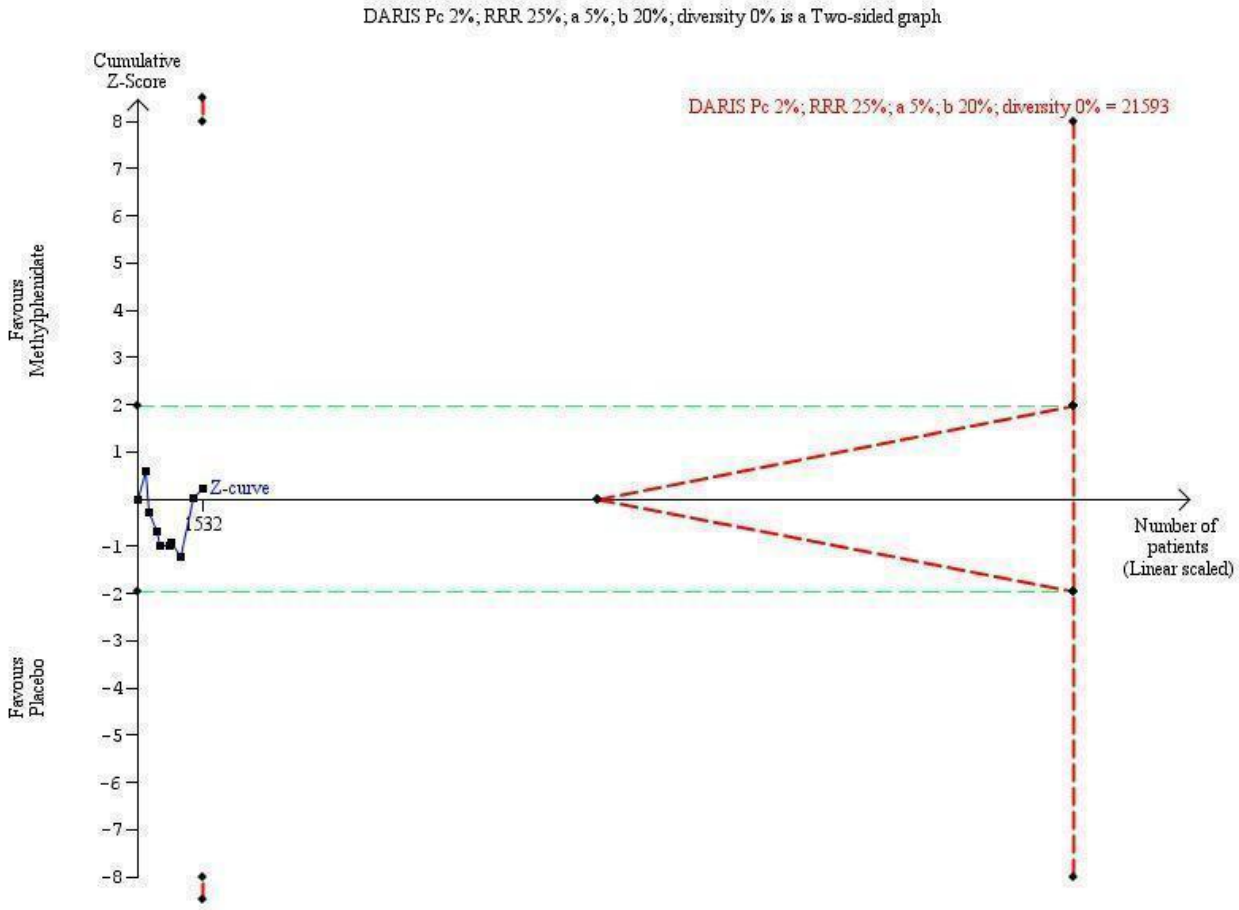
## Figure 4 (Analysis 1.11)




*Caption*

Funnel plot of comparison: 1. Teacher-rated ADHD symptoms, outcome: 1.8 All data at low and high risk of bias (parallel-group and cross-over trials).

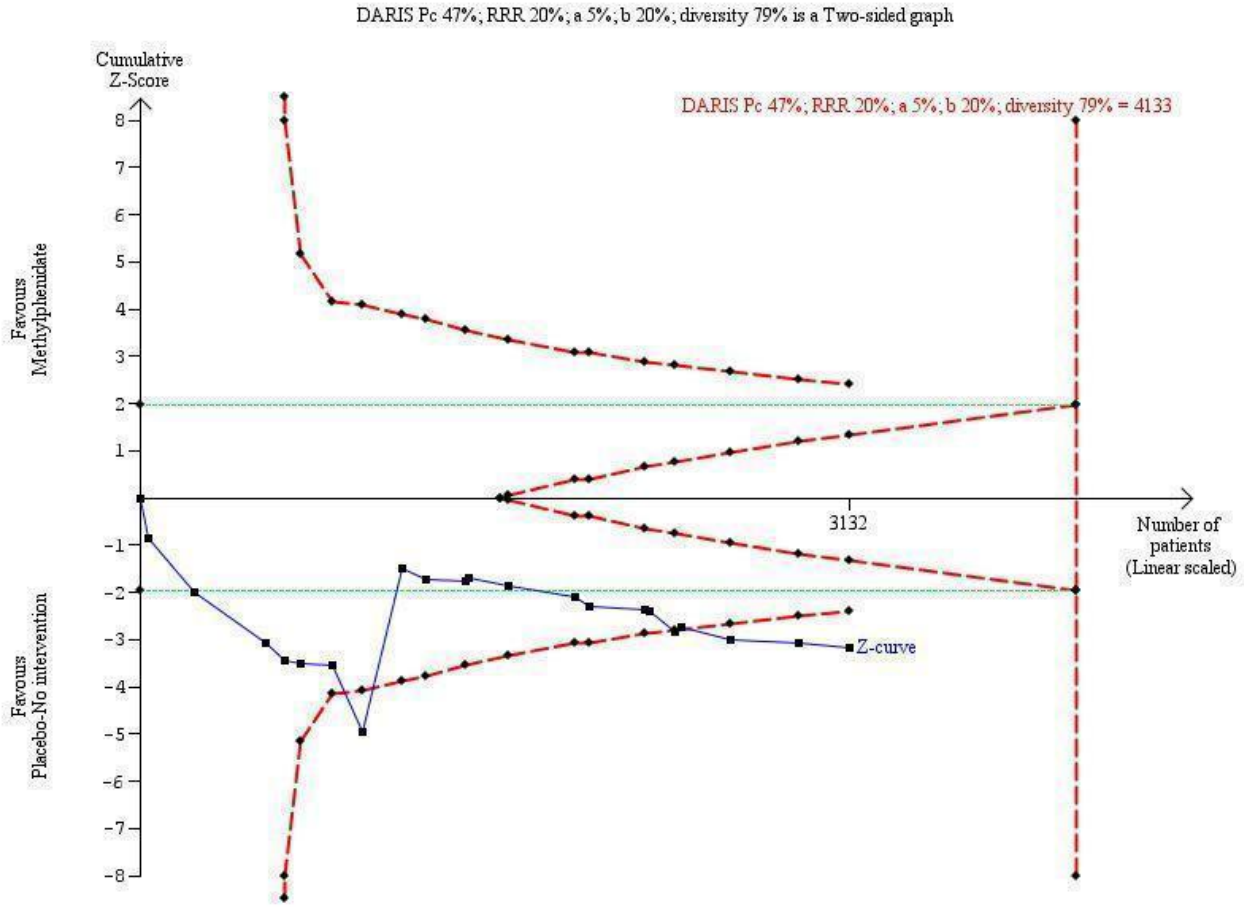
## Figure 5




*Caption*

Trial Sequential Analysis: serious adverse events.

## Figure 6




*Caption*

Trial Sequential Analysis: non-serious adverse events.

# Sources of support

## Internal sources

- Psychiatric Research Unit, Region Zealand Psychiatry, Roskilde, Denmark
  Ole Jakob Storebø, Erica Ramstad, Helle B. Krogh, Trine Danvad Nilausen, Mathilde Holmskov, Frederik Løgstrup Magnusson, and Erik Simonsen worked on this review during office hours
- Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital, Denmark
  Maria Skoog and Christian Gluud worked on this review during office hours

## External sources

- Region Zealand Research Foundation, Denmark
  This review is supported by a grant (DKR 532,901) from the Region Zealand Research Foundation

# Feedback

# Appendices

## 1 Search strategies

| Database | Search strategy |
|---|---|
| CENTRAL (*Cochrane Library*) | **Efficacy**<br>#1 MeSH descriptor Methylphenidate explode all trees<br>#2 Methylphenidate<br>#3 Attenta<br>#4 Biphentin<br>#5 Calocain<br>#6 Centedrin*<br>#7 Concerta<br>#8 Daytrana<br>#9 Dexmethylphenidat*<br>#10 Equasym |

#11 Focalin
#12 Medikinet
#13 Meridil
#14 Metadate
#15 Methyl phenidat*
#16 Methyl phenidylacetat*
#17 Methylfenid*
#18 Methylin
#19 Methylofenidan
#20 Methylphenid*
#21 Methyl phenidyl acetat*
#22 Methypatch
#23 Metilfenidato
#24 Motiron
#25 MPH
#26 Penid
#27 Phenidyl hydrochlorid*
#28 Phenidylat*
#29 Plimasin*
#30 PMS-Methylphenid*
#31 Richter Works
#32 Riphenidat*
#33 Ritalin*
#34 Rubifen
#35 Stimdat*
#36 Tsentedrin*
#37 Elmifiten or Medikid or Omozin or Quazym or Tifinidat or Tranquilyn
#38 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37)
#39 MeSH descriptor Child explode all trees
#40 MeSH descriptor Adolescent explode all trees
#41 MeSH descriptor Infant explode all trees
#42(child* OR boy* OR girl* OR adolescen* OR teen* OR preschool OR pre school OR infant* OR baby OR babies OR toddler* OR school child* or youth*)
#43 (#39 OR #40 OR #41 OR #42)
#44 (#38 AND #43)
#45 MeSH descriptor Attention Deficit and Disruptive Behavior Disorders explode all trees
#46 (ADHD):ti,ab,kw
#47 (ADDH):ti,ab,kw
#48 (ADHS):ti,ab,kw
#49 ("AD/HD"):ti,ab,kw
#50 ((attention* or behav*) near/3 (defic* or dysfunc* or disorder*)):ti,ab,kw
#51 (impulsiv* or inattentiv* or inattention*):ti,ab,kw
#52 ((disrupt* near/3 disorder*) or (disrupt* near/3 behav*) or (defian* near/3 disorder*) or (defian* near/3 behav*)):ti,ab,kw
#53 MeSH descriptor Hyperkinesis explode all trees
#54 (hyperkine*):ti,ab,kw
#55 ((minimal near/3 brain near/3 (disorder* or dysfunct* or damage*))):ti,ab,kw
#56 (hyperactiv*):ti,ab,kw
#57 (#45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56)
#58 (#44 AND #57)

Adverse events
#1 MeSH descriptor Methylphenidate explode all trees
#2 Methylphenidate
#3 Attenta
#4 Biphentin
#5 Calocain
#6 Centedrin*
#7 Concerta
#8 Daytrana
#9 Dexmethylphenidat*
#10 Equasym
#11 Focalin
#12 Medikinet
#13 Meridil

| | |
|---|---|
| | #14 Metadate<br>#15 Methyl phenidat*<br>#16 Methyl phenidylacetat*<br>#17 Methylfenid*<br>#18 Methylin<br>#19 Methylofenidan<br>#20 Methylphenid*<br>#21 Methyl phenidyl acetat*<br>#22 Methypatch<br>#23 Metilfenidato<br>#24 Motiron<br>#25 MPH<br>#26 Penid<br>#27 Phenidyl hydrochlorid*<br>#28 Phenidylat*<br>#29 Plimasin*<br>#30 PMS-Methylphenid*<br>#31 Richter Works<br>#32 Riphenidat*<br>#33 Ritalin*<br>#34 Rubifen<br>#35 Stimdat*<br>#36 Tsentedrin*<br>#37 elmifiten or medikid or Omozin or Quazym or Tifinidat or Tranquilyn<br>#38 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR (#29 AND # ) OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37)<br>#39 Any MeSH descriptor with qualifiers: AE,DE,CI<br>#40 (safe or safety or adverse or tolerability or toxicity or toxic or adrs or adr or tolerance or tolerate or harm or harms or harmful or complication* or risk or risks):ti,ab<br>#41 (side next effect):ti,ab<br>#42 (undesirable next effect):ti,ab<br>#43 (treatment next emergent):ti,ab<br>#44(unintended next event):ti,ab<br>#45 (unintended next effect):ti,ab<br>#46 (#39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45)<br>#47 MeSH descriptor Child explode all trees<br>#48 MeSH descriptor Adolescent explode all trees<br>#49 MeSH descriptor Infant explode all trees<br>#50 (child* OR boy* OR girl* OR adolescen* OR teen* OR preschool OR pre school OR infant* OR baby OR babies OR toddler* OR school child* or youth*)<br>#51 MeSH descriptor Mood Disorders explode all trees<br>#52 (depression):ti,ab,kw or (depressive):ti,ab,kw<br>#53 MeSH descriptor Psychotic Disorders explode all trees<br>#54 (psychosis or (psychotic near/4 symptom*)):ti,ab,kw<br>#55 MeSH descriptor Body Weight explode all trees<br>#56 MeSH descriptor Anorexia explode all trees<br>#57 ((loss or lose or losing or decreas* or reduc*) near/3 (weight or appetite)):ti,ab,kw<br>#58 (loss near/3 weight):ti,ab,kw<br>#59 ((reduc* or retard* or inhibit* or deficit*) near/4 growth):ti,ab,kw<br>#60 MeSH descriptor Hypertension explode all trees<br>#61 MeSH descriptor Heart Rate explode all trees<br>#62 MeSH descriptor Tachycardia explode all trees<br>#63 (increas* near/4 (heart rate or pulse or blood pressure)):ti,ab,kw<br>#64 MeSH descriptor Death, Sudden explode all trees<br>#65 (death):ti,ab,kw<br>#66 MeSH descriptor Infertility explode all trees<br>#67 (((loss or reduc*) near/4 fertility) or infertility):ti,ab,kw<br>#68 MeSH descriptor Carcinogens explode all trees<br>#69 MeSH descriptor Neoplasms explode all trees<br>#70 ((risk near/2 cancer) or (cytogenetic near/2 effect*)):ti,ab,kw<br>#71 (#46 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70)<br>#72 (#47 OR #48 OR #49 OR #50)<br>#73 (#38 AND #71 AND #72) |
| Ovid MEDLINE | |

**Efficacy**

1. exp “attention deficit and disruptive behavior disorders”/
2. adhd.mp.
3. addh.mp.
4. adhs.mp.
5. (ad adj hd).mp.
6. ((attention* or behav*) adj3 (defic* or dysfunc* or disorder*)).mp.
7. ((disrupt* adj3 disorder*) or (disrupt* adj3 behav*) or (defian* adj3 disorder*) or (defian* adj3 behav*)).mp.
8. (impulsiv* or inattentiv* or inattention*).mp.
9. hyperactiv*.mp.
10. hyperkinesis*.mp.
11. exp Hyperkinesis/
12. (minimal adj brain adj3 disorder*).mp.
13. (minimal adj brain adj3 dysfunction*).mp.
14. (minimal adj brain adj3 damage*).mp.
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. randomized controlled trial.pt.
17. controlled clinical trial.pt.
18. randomized controlled trials.mp.
19. random allocation.mp.
20. double blind method.mp.
21. single blind method.mp.
22. clinical trial.pt.
23. (clin* adj25 trial*).ti,ab.
24. ((singl* or doubl* or tripl* or trebl*) adj25 (blind* or mask* or dummy*)).mp.
25. exp Clinical Trial/
26. placebos.mp.
27. placebo*.ti,ab.
28. random*.ti,ab.
29. comparative trial.mp.
30. Evaluation Studies as Topic/
31. exp Clinical Trials as Topic/
32. follow up studies.mp.
33. prospective studies.mp.
34. (control* or prospectiv* or volunteer*).ti,ab.
35. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36. 15 and 35
37. Methylphenidate.mp. or Methylphenidate/
38. Attenta.mp.
39. Biphentin.mp.
40. Calocain.mp.
41. Centedrin*.mp.
42. Concerta.mp.
43. Daytrana.mp.
44. Dexmethylphenidat*.mp.
45. Elmifiten.mp.
46. Equasym.mp.
47. Focalin.mp.
48. Medikid.mp.
49. Medikinet.mp.
50. Meridil.mp.
51. Metadate.mp.
52. Methyl phenidat*.mp.
53. Methyl phenidylacetat*.mp.
54. Methylfenid*.mp.
55. Methylin.mp.
56. Methylofenidan.mp.
57. Methylphenid*.mp.
58. Methyl phenidyl acetat*.mp.
59. Methypatch.mp.
60. Metilfenidato.mp.
61. Motiron.mp.
62. MPH.mp.
63. Penid.mp.

64. Omozin.mp.
65. Quazym.mp.
66. Phenidyl hydrochlorid*.mp.
67. Phenidylat*.mp.
68. Plimasin*.mp.
69. PMS-Methylphenid*.mp.
70. Richter Works.mp.
71. Riphenidat*.mp.
72. Ritalin*.mp.
73. Rubifen.mp.
74. Stimdat*.mp.
75. Tifinidat.mp.
76. Tranquilyn.mp.
77. Tsentedrin*.mp.
78. 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77
79. 36 and 78
80. exp Child/
81. exp Adolescent/
82. exp Infant/
83. (child* or boy* or girl* or adolescen* or teen* or preschool or pre school or infant* or baby or babies or toddler* or school child* or youth*).mp.
84. 80 or 81 or 82 or 83
85. 79 and 84
86. 85 and 79 and 84

**Adverse events**

1. Methylphenidate.mp. or Methylphenidate/
2. Attenta.mp.
3. Biphentin.mp.
4. Calocain.mp.
5. Centedrin*.mp.
6. Concerta.mp.
7. Daytrana.mp.
8. Dexmethylphenidat*.mp.
9. Elmifiten.mp.
10. Equasym.mp.
11. Focalin.mp.
12. Medikid.mp.
13. Medikinet.mp.
14. Meridil.mp.
15. Metadate.mp.
16. Methyl phenidat*.mp.
17. Methyl phenidylacetat*.mp.
18. Methylfenid*.mp.
19. Methylin.mp.
20. Methylofenidan.mp.
21. Methylphenid*.mp.
22. Methyl phenidyl acetat*.mp.
23. Methypatch.mp.
24. Metilfenidato.mp.
25. Motiron.mp.
26. MPH.mp.
27. Omozin.mp.
28. Penid.mp.
29. Phenidyl hydrochlorid*.mp.
30. Phenidylat*.mp.
31. Plimasin*.mp.
32. PMS-Methylphenid*.mp.
33. Richter Works.mp.
34. Quazym.mp.
35. Riphenidat*.mp.
36. Ritalin*.mp.
37. Rubifen.mp.
38. Stimdat*.mp.
39. Tifinidat.mp.

| | |
|---|---|
| | 40. Tranquilyn.mp.<br>41. Tsentedrin*.mp.<br>42. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41<br>43. (ae or co or de).fs.<br>44. (safe or safety or (side adj1 effect*) or (undesirable adj1 effect*) or (treatment adj1 emergent) or tolerability or tolerance or tolerate or toxicity or toxic or adrs or adr or harm or harms or harmful or complication* or risk or risks or (unintended adj1 event*) or (unintended adj1 effect*)).ti,ab.<br>45. (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.<br>46. 43 or 44 or 45<br>47. exp Child/<br>48. exp Adolescent/<br>49. exp Infant/<br>50. (child* or boy* or girl* or adolescen* or teen* or preschool or pre school or infant* or baby or babies or toddler* or school child* or youth*).mp.<br>51. 47 or 48 or 49 or 50<br>52. exp Mood Disorders/<br>53. (depression or depressive).ti,ab.<br>54. exp Psychotic Disorders/<br>55. (psychosis or (psychotic adj4 symptom*)).ti,ab.<br>56. exp Body Weight/ or Anorexia/<br>57. ((loss or lose or losing or reduc*) adj3 (weight or appetite)).ti,ab.<br>58. ((reduc* or retard* or inhibit* or deficit*) adj4 growth).ti,ab.<br>59. exp Hypertension/<br>60. Heart Rate/<br>61. exp tachycardia/<br>62. (increas* adj4 (heart rate or pulse or blood pressure)).ti,ab.<br>63. exp Death, Sudden/<br>64. death.ti,ab.<br>65. exp Infertility/<br>66. (((loss or reduc*) adj4 fertility) or infertility).ti,ab.<br>67. exp Carcinogens/<br>68. exp Neoplasms/<br>69. ((risk adj2 cancer) or (cytogenetic adj2 effect*)).ti,ab.<br>70. 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69<br>71. 46 or 70<br>72. 42 and 51 and 71<br>73. Methylphenidate/ae, po, to<br>74. 51 and 73<br>75. 72 or 74 |
| EMBASE (Ovid) | **Efficacy**<br>1. exp Attention Deficit Disorder/<br>2. adhd.ti,ab.<br>3. addh.ti,ab.<br>4. ADHS.ti,ab.<br>5. (AD adj HD).ti,ab.<br>6. ((disrupt* adj3 disorder*) or (disrupt* adj3 behav*) or (defian* adj3 disorder*) or (defian* adj3 behav*)).ti,ab.<br>7. ((attention* or behav*) adj3 (defic* or dysfunc* or disorder*)).ti,ab.<br>8. (impulsiv* or inattentiv* or inattention*).ti,ab.<br>9. exp Hyperactivity/<br>10. Hyperkinesia/<br>11. hyperactiv*.ti,ab.<br>12. hyperkinesis*.ti,ab.<br>13. (minimal adj brain adj3 disorder*).ti,ab.<br>14. (minimal adj brain adj3 dysfunction*).ti,ab.<br>15. (minimal adj brain adj3 damage*).ti,ab.<br>16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or<br>13 or 14 or 15<br>17. controlled trial.de.<br>18. clinical trial.de.<br>19. major clinical trial.de.<br>20. randomized controlled trial.de. |

21. double blind procedure.de.
22. clinical article.de.
23. random*.mp.
24. control*.mp.
25. follow up.mp.
26. ((singl* or doubl* or tripl* or trebl*) adj (blind* or mask* or dummy)).mp.
27. placebo*.mp.
28. (clinic* adj (trial* or trial or studies*)).mp.
29. exp comparative trial/
30. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31. 16 and 30
32. methylphenidate.mp. or METHYLPHENIDATE/
33. Attenta.mp.
34. Biphentin.mp.
35. Calocain.mp.
36. Centedrin*.mp.
37. Concerta.mp.
38. Daytrana.mp.
39. Dexmethylphenidat*.mp.
40. Elmifiten.mp.
41. Equasym.mp.
42. Focalin.mp.
43. Medikid.mp.
44. Medikinet.mp.
45. Meridil.mp.
46. Metadate.mp.
47. Methyl phenidat*.mp.
48. Methyl phenidylacetat*.mp.
49. Methylfenid*.mp.
50. Methylin.mp.
51. Methylofenidan.mp.
52. Methylphenid*.mp.
53. Methyl phenidyl acetat*.mp.
54. Methypatch.mp.
55. Metilfenidato.mp.
56. Motiron.mp.
57. MPH.mp.
58. Omozin.mp.
59. Penid.mp.
60. Phenidyl hydrochlorid*.mp.
61. Phenidylat*.mp.
62. Plimasin*.mp.
63. PMS-Methylphenid*.mp.
64. Quazym.mp.
65. Richter Works.mp.
66. Riphenidat*.mp.
67. Ritalin*.mp.
68. Rubifen.mp.
69. Stimdat*.mp.
70. Tifinidat.mp.
71. Tranquilyn.mp.
72. Tsentedrin*.mp.
73. 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72
74. 31 and 73
75. exp child/
76. exp adolescent/
77. (child* or boy* or girl* or adolescen* or teen* or preschool or pre school or infant* or baby or babies or toddler* or school child* or youth*).mp.
78. 75 or 76 or 77
79. 74 and 78

**Adverse events**

1 Methylphenidate.mp.
2 Attenta.mp.
3 Biphentin.mp.

4 Calocain.mp.
5 Centedrin*.mp.
6 Concerta.mp.
7 Daytrana.mp.
8 Dexmethylphenidat*.mp.
9 Elmifiten.mp.
10 Equasym.mp.
11 Focalin.mp.
12 Medikid.mp.
13 Medikinet.mp.
14 Meridil.mp.
15 Metadate.mp.
16 Methyl phenidat*.mp.
17 Methyl phenidylacetat*.mp.
18 Methylfenid*.mp.
19 Methylin.mp.
20 Methylofenidan.mp.
21 Methylphenid*.mp.
22 Methyl phenidyl acetat*.mp.
23 Methypatch.mp.
24 Metilfenidato.mp.
25 Motiron.mp.
26 MPH.mp.
27 Omozin.mp.
28 Penid.mp.
29 Phenidyl hydrochlorid*.mp.
30 Phenidylat*.mp.
31 Plimasin*.mp.
32 PMS-Methylphenid*.mp.
33 Richter Works.mp.
34 Riphenidat*.mp.
35 Ritalin*.mp.
36 Rubifen.mp.
37 Tifinidat.mp.
38 Stimdat*.mp.
39 Tranquilyn.mp.
40 Tsentedrin*.mp.
41 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40
42 (safe or safety or (side adj1 effect*) or (undesirable adj1 effect*) or (treatment adj1 emergent) or tolerability or tolerance or tolerate or toxicity or toxic or adrs or adr or harm or harms or harmful or complication* or risk or risks or (unintended adj1 event*) or (unintended adj1 effect*)).ti,ab.
43 (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.
44 exp adverse drug reaction/
45 exp side-effect/
46 42 or 43 or 44 or 45
47 methylphenidate/ae, to
48 exp mood disorder/si
49 (depression or depressive).ti,ab.
50 exp psychosis/si
51 (psychosis or (psychotic adj4 symptom*)).ti,ab.
52 growth retardation/ or growth inhibition/
53 ((loss or lose or losing or reduc*) adj3 weight).ti,ab.
54 ((reduc* or retard* or inhibit* or deficit*) adj4 growth).ti,ab.
55 hypertension/si
56 heart rate/
57 cardiovascular effect/
58 tachycardia/si
59 (increas* adj4 (heart rate or pulse or blood pressure)).ti,ab.
60 Sudden death/
61 death.ti,ab.
62 infertility/si
63 (((loss or reduc*) adj4 fertility) or infertility).ti,ab.
64 cancer risk/

| | |
|---|---|
| | 65 carcinogenicity/<br>66 chromosome aberration/si<br>67 childhood cancer/si<br>68 ((risk adj2 cancer) or (cytogenetic adj2 effect*)).ti,ab.<br>69 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68<br>70 exp child/<br>71 exp adolescent/<br>72 (child* or boy* or girl* or adolescen* or teen* or preschool or pre school or infant* or baby or babies or toddler* or school child* or youth*).mp.<br>73 70 or 71 or 72<br>74 46 or 69<br>75 41 and 74<br>76 47 or 75<br>77 73 and 76 |
| CINAHL (EBSCOhost) | **Broad strategy to capture both efficacy and adverse events studies**<br>S43 S37 and S42<br>S42 S38 or S39 or S40 or S41<br>S41 (child* OR boy* OR girl* OR adolescen* OR teen* OR preschool OR pre school OR infant* OR baby OR babies OR toddler* OR school child* or youth*)<br>S40 (MH "Adolescence+")<br>S39 (MH "Infant+")<br>S38 (MH "Child+")<br>S37 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36<br>S36 Tsentedrin* or Tranquilyn<br>S35 Stimdat* or Tifinidat<br>S34 Rubifen<br>S33 Ritalin*<br>S32 Riphenidat*<br>S31 Richter Works<br>S30 PMS-Methylphenid* or Quazym<br>S29 Plimasin*<br>S28 Phenidylat*<br>S27 Phenidyl hydrochlorid*<br>S26 Penid or Omozin<br>S25 MPH<br>S24 Motiron<br>S23 Metilfenidato<br>S22 Methypatch<br>S21 Methyl phenidyl acetat*<br>S20 Methylphenid*<br>S19 Methylofenidan<br>S18 Methylin<br>S17 Methylfenid*<br>S16 Methyl phenidylacetat*<br>S15 Methyl phenidat*<br>S14 Metadate<br>S13 Meridil<br>S12 Medikinet<br>S11 Focalin or Medikid<br>S10 Equasym<br>S9 Dexmethylphenidat* or Elmifiten<br>S8 Daytrana<br>S7 Concerta<br>S6 Centedrin*<br>S5 Calocain<br>S4 Biphentin<br>S3 Attenta<br>S2 Methylphenidate<br>S1 (MH "Methylphenidate") |
| PsycINFO (Ovid) | **Efficacy**<br>1. exp attention deficit disorder/ |

2. adhd.ti,ab.
3. addh.ti,ab.
4. ADHS.ti,ab.
5. (AD adj HD).ti,ab.
6. ((attention* or behav*) adj3 (defic* or dysfunc* or disorder*)).ti,ab.
7. ((disrupt* adj3 disorder*) or (disrupt* adj3 behav*) or (defian* adj3 disorder*) or (defian* adj3 behav*)).ti,ab.
8. (impulsiv* or inattentiv* or inattention*).ti,ab.
9. hyperactiv*.ti,ab.
10. hyperkinesis*.ti,ab.
11. exp Hyperkinesis/
12. (minimal adj brain adj3 disorder*).ti,ab.
13. (minimal adj brain adj3 dysfunction*).ti,ab.
14. (minimal adj brain adj3 damage*).ti,ab.
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. random*.mp.
17. ((singl* or doubl* or trebl* or tripl*) adj25 (blind* or dummy or mask*)).mp.
18. placebo*.mp.
19. crossover.mp.
20. assign*.mp.
21. allocat*.mp.
22. ((clin* or control* or compar* or evaluat* or prospectiv*) adj25 (trial* or studi* or trial)).mp.
23. exp placebo/
24. exp treatment effectiveness evaluation/
25. exp mental health program evaluation/
26. exp experimental design/
27. versus.id.
28. vs.id.
29. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 15 and 29
31. Methylphenidate.mp. or Methylphenidate/
32. Attenta.mp.
33. Biphentin.mp.
34. Calocain.mp.
35. Centedrin*.mp.
36. Concerta.mp.
37. Daytrana.mp.
38. Dexmethylphenidat*.mp.
39. Elmifiten.mp.
40. Equasym.mp.
41. Focalin.mp.
42. Medikid.mp.
43. Medikinet.mp.
44. Meridil.mp.
45. Metadate.mp.
46. Methyl phenidat*.mp.
47. Methyl phenidylacetat*.mp.
48. Methylfenid*.mp.
49. Methylin.mp.
50. Methylofenidan.mp.
51. Methylphenid*.mp.
52. Methyl phenidyl acetat*.mp.
53. Methypatch.mp.
54. Metilfenidato.mp.
55. Motiron.mp.
56. MPH.mp.
57. Omozin.mp.
58. Penid.mp.
59. Phenidyl hydrochlorid*.mp.
60. Phenidylat*.mp.
61. Plimasin*.mp.
62. PMS-Methylphenid*.mp.
63. Quazym.mp.
64. Richter Works.mp.
65. Riphenidat*.mp.
66. Ritalin*.mp.

67. Rubifen.mp.
68. Stimdat*.mp.
69. Tifinidat.mp.
70. Tranquilyn.mp.
71. Tsentedrin*.mp.
72. 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 73. 30 and 72
74. (child* or boy* or girl* or adolescen* or teen* or preschool or pre school or infant* or baby or babies or toddler* or school child* or youth*).mp.
75. 73 and 74

**Adverse events**

1. Methylphenidate.mp. or Methylphenidate/
2. Attenta.mp.
3. Biphentin.mp.
4. Calocain.mp.
5. Centedrin*.mp.
6. Concerta.mp.
7. Daytrana.mp.
8. Dexmethylphenidat*.mp.
9. Elmifiten.mp.
10. Equasym.mp.
11. Focalin.mp.
12. Medikid.mp.
13. Medikinet.mp.
14. Meridil.mp.
15. Metadate.mp.
16. Methyl phenidat*.mp.
17. Methyl phenidylacetat*.mp.
18. Methylfenid*.mp.
19. Methylin.mp.
20. Methylofenidan.mp.
21. Methylphenid*.mp.
22. Methyl phenidyl acetat*.mp.
23. Methypatch.mp.
24. Metilfenidato.mp.
25. Motiron.mp.
26. MPH.mp.
27. Omozin.mp.
28. Penid.mp.
29. Phenidyl hydrochlorid*.mp.
30. Phenidylat*.mp.
31. Plimasin*.mp.
32. PMS-Methylphenid*.mp.
33. Quazym.mp.
34. Richter Works.mp.
35. Riphenidat*.mp.
36. Ritalin*.mp.
37. Rubifen.mp.
38. Stimdat*.mp.
39. Tifinidat.mp.
40. Tranquilyn.mp.
41. Tsentedrin*.mp.
42. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
43. "Side effects (Drug)"/
44. (safe or safety or (side adj1 effect*) or (undesirable adj1 effect*) or (treatment adj1 emergent) or tolerability or tolerance or tolerate or toxicity or toxic or adrs or adr or harm or harms or harmful or complication* or risk or risks or (unintended adj1
event*) or (unintended adj1 effect*)).ti,ab.
45. (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.
46. 43 or 44 or 45
47. exp major depression/ or affective disorders/
48. (depression or depressive).ti,ab.

| | |
|---|---|
| | 49. exp psychosis/<br>50. (psychosis or (psychotic adj4 symptom*)).ti,ab.<br>51. exp body weight/<br>52. exp appetite depressing drugs/<br>53. Appetite/<br>54. ((loss or lose or losing or decreas* or reduc*) adj3 (weight or appetite)).ti,ab.<br>55. ((reduc* or retard* or inhibit* or deficit*) adj4 growth).ti,ab.<br>56. exp appetite depressing drugs/<br>57. Appetite/<br>58. exp cardiovascular disorders/<br>59. exp heart rate affecting drugs/<br>60. Heart rate/<br>61. (increas* adj4 (heart rate or pulse or blood pressure)).ti,ab.<br>62. "death and dying"/<br>63. death.ti,ab.<br>64. exp infertility/<br>65. (((loss or reduc*) adj4 fertility) or infertility).ti,ab.<br>66. exp neoplasms/<br>67. Carcinogens/<br>68. ((risk adj2 cancer) or (cytogenetic adj2 effect*)).ti,ab.<br>69. 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68<br>70. 46 or 69<br>71. 42 and 70<br>72. (child* or boy* or girl* or adolescen* or teen* or preschool or pre school or infant* or baby or babies or toddler* or school child* or youth*).mp.<br>73. 71 and 72 |
| CPCI-S, CPCI-SSH<br><br>(Web of Science) | **Broad strategy to capture both efficacy and adverse events studies**<br><br>#2 AND #1<br><br>#2 TS=(child* or boy* or girl* or adolescen* or teen* or preschool* or "pre school*" or infant* or baby or babies or toddler* or "school child*" or schoolchild* or youth*)<br><br>#1 TS=(Methylphenidate or Attenta or Biphentin or Calocain or Centedrin* or Concerta or Daytrana or Dexmethylphenidat* or Elmifiten or Equasym or Focalin or Medikid or Medikinet or Meridil or Metadate or "Methyl phenidat*" or "Methyl phenidylacetat" or Methylfenid or Methylin or Methylofenidan or Methylphenid* or "Methyl phenidyl acetat*" or Methypatch or Metilfenidato or Motiron or MPH or Penid or Omozin or Quazym or "Phenidyl hydrochlorid*" or Phenidylat* or Plimasin* or "PMS-Methylphenid* " or "Richter Works" or Riphenidat* or Ritalin* or Rubifen or Stimdat* or Tifinidat or Tranquilyn or Tsentedrin*) |
| ClinicalTrials.gov | Advanced search: Methylphenidate OR concerta OR daytrana OR dexmethylphenidate OR equasym OR focalin OR medikinet OR MPH OR Ritalin<br><br>Studies with results<br><br>Age group: Child |
| WHO ICTRP ( who.int/ictrp/en | Intervention: Methylphenidate OR concerta OR daytrana OR dexmethylphenidate OR equasym OR focalin OR medikinet OR MPH OR Ritalin<br><br>Status: all<br><br>Children |

CENTRAL: Cochrane Central Register of Controlled Trials.
CINAHL: Cumulative Index to Nursing and Allied Health Literature.
CPCI-S: Conference Proceedings Citation Index - Science.
CPCI-SSH: Conference Proceedings Citation Index - Social Science & Humanities.
WHO ICTRP: World Health Organisation International Clinical Trials Registry Platform.

## 2 Letter to pharmaceutical companies

To whom it might concern,

Date: June 2013

**The Cochrane Methylphenidate Group**

Psychiatric Research Unit

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4000 Roskilde, Denmark

**Ole Jakob Storebø**

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Web: regionsjaelland.dk/psykforsk

***Regarding: Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents – a Cochrane systematic review.***

On behalf of the Cochrane Methylphenidate Group we address you in order to request your assistance. We are elaborating a systematic review on the effect of methylphenidate treatment for children and adolescents with ADHD. We have been entrusted the elaboration of this review by *The Cochrane Developmental, Psychosocial and Learning Problems Group*.

The Cochrane systematic review intends to include all relevant literature empirically describing both the positive and possibly negative effects of the medical treatment. We believe the elaboration of this review is in common interest of patients, doctors and manufacturers of methylphenidate. Furthermore, it is an important ethical issue. The results from this review will, in the future, guide authorities, clinicians and researchers when it comes to considering the use of methylphenidate in the treatment for children and adolescents with ADHD.

The Cochrane review will be comprehensive. The currently included studies come from our search for literature through international, scientific databases [1]. However, the published literature only provides us with limited and possibly selective knowledge, since it is unlikely that all studies and data are available through these databases. By contacting authors of significant publications, experts in the field and pharmaceutical companies, we hope to be informed of additional studies, published as well as unpublished. We have been inspired by this approach used in other Cochrane systematic reviews investigating medical preparations for other widespread diseases as ADHD.

We hope you will assist us with providing data that are relevant for our review. As previously noted, we are interested in data regarding both positive and negative effects of methylphenidate from both observational studies and randomised clinical trials, regardless of the year the data were recorded or published.

It is important for us to point out that we are not investigating specific methylphenidate preparations but simply the effect of the active substance, methylphenidate. Thus, we will not refer to or recommend any specific methylphenidate preparation or drug company. However, we will state which companies we have been in contact with, and which of these who have assisted us with data.

If possible, we would be very pleased to meet a representative from your company.

Enclosed to this letter are our protocol, a recommendation from *The Cochrane Developmental, Psychosocial and Learning Problems Group* and a list of the currently included studies in our review.

We are hoping to hear from you. If you have any questions, please contact us.

On behalf of

**The Cochrane Developmental, Psychosocial and Learning Problems Group**

**The Cochrane Methylphenidate Group**

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Erik Simonsen
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*Toftebakken 9, 4000 Roskilde, Denmark*

Christian Gluud
*MD, dr. Med. Sci.,*
*Head of Department, Copenhagen Trial Unit,*
*Centre for Clinical Intervention Research,*
*Copenhagen University Hospital, Denmark*

Per Hove Thomsen

*Professor, MD, DMSc*
*Department of Children and Youth Psychiatry, Aarhus University Hospital*

[1] Cochrane Central Register of Controlled Trials (CENTRAL) part of *The Cochrane Library,* MEDLINE, PsycINFO, EMBASE, CINAHL, ISI Conference Proceedings Citation Index (Science, and Social Science and Humanities), Clinical Trials.gov, and International Clinical Trials Registry Platform (ICTRP)

## 3 Data extraction sheet RCTs - parallel-group trials

***Version 09.04.2014***

### Source

| |
|---|
| Trial ID (e.g. Plizska 2000) |
| Trial registry with ID *Search* clinicaltrials.gov *(from 2008 -) and* who.int/ictrp/en *(from 2004 -)* |
| Full citation |
| Form filled by |
| Author contact information |
| Other publications on same trial |

ID: identifier.

### Eligibility

| | |
|---|---|
| Confirm eligibility | Yes No Awaiting assessment |

### Correspondence

| |
|---|
| Correspondence required |

### Method

| | |
|---|---|
| Cluster-randomised | Yes/no<br>Intervention (n (number)) =, control (n) = |
| Location (e.g. hospital, out-clinic) | - |
| Summary (method) | Parallel trial with 2 arms:<br>1. Methylphenidate<br>2. Control |

### Participants

| | |
|---|---|
| Summary (participants) | Number of participants screened |
| | Number of participants included |
| | Number of participants randomly assigned to methylphenidate and control |
| | Number of participants followed up in each arm: methylphenidate and control |
| | Number of withdrawals in each arm: Methylphenidate and control |
| | *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (DSM-III) diagnosis of attention deficit hyperactivity disorder (ADHD) (combined (%), hyperactive-impulsive (%), inattentive (%)) |
| | Age (years) (mean, range) |
| | IQ (mean, range) |
| | Sex (male, female) |
| | Methylphenidate naive (%/number) |
| | Ethnicity (Caucasian (%), African American (%), Asian (%), Hispanic (%), other (%)) |
| | Country |
| | Comorbidity (type %) |
| | Comedication (no/yes) |
| | Sociodemographics (e.g. double or single parent family, low, middle or upper class) |
| | Inclusion criteria |
| | Exclusion criteria |

## Interventions

Participants were randomly assigned to type of (e.g. immediate-release (IR), extended-release (ER)) (dex-) methylphenidate or control
Methylphenidate dosage: Mean (standard deviation (SD))
Administration schedule: time points
Duration of intervention
Titration period: none/duration initiated before/after randomisation
Treatment compliance

## Outcome listing

(Our outcomes according to our protocol: short, general description)

ADHD symptoms

Measure instrument (e.g. ADHD Rating Scale (ADHD-RS); Swanson, Kotkin, Atkins, M-Flynn and Pelham (SKAMP) Scale), parent-/teacher-/independent assessor-rated, time point

General behaviour

Measure instrument (e.g. Child Behavior Checklist (CBCL)), parent-/teacher-/independent assessor-rated, time point

Quality of life

Measure instrument, parent-/teacher-/independent assessor-rated, time point

Serious adverse events

Type of outcome/adverse event, measure method/instrument, parent-/teacher-/independent assessor-rated, time point

Non-serious adverse events

Type of outcome/adverse event, measure method/instrument, parent-/teacher-/independent assessor-rated, time point

**Outcomes (positive effects)**

*e.g. copy of table from article*

**Outcomes (adverse events)**

*e.g. copy of table from article*

| Outcomes specified | Type of adverse events/responses | Total numbers | Mean | SD | Time point |
|---|---|---|---|---|---|
| Serious adverse events (temporal association, but not necessarily causal relationship) | | | | | |
| Serious adverse reaction (response to the drug) | | | | | |
| Non-serious adverse events (temporal association) | | | | | |

## Risk of bias

| Item | Quote | Risk of bias (high, unclear, low) |
|---|---|---|
| Random sequence generation/generation of allocation sequence (selection bias) | | |
| Allocation concealment (selection bias) | | |
| Blinding of participants and personnel (performance bias) | | |
| Blinding of outcome assessment (detection bias) | | |
| Incomplete outcome data (intention-to-treat (ITT), imputation method) (attrition bias) | | |
| Selective outcome reporting (according to protocol?) | | |
| Vested interest | | |
| Other sources of bias | Authors' affiliations (e.g. Novartis)<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders) | |

Notes

| |
|---|
| Sample calculation |
| Ethics approval |
| Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate |
| Any withdrawals due to adverse events |
| Comments from trial authors |
| Key conclusions of trial authors |
| Comments from review authors |
| Supplemental information/data received through personal email correspondence with trial authors in *month* 2014 |

## 4 Data extraction sheet RCTs - cross-over trials

***Version 09.04.2014***

Source

| | |
|---|---|
| Trial ID (e.g. Plizska 2000) | |
| Trial registry with ID *Search* clinicaltrials.gov *(from 2008 -) and* who.int/ictrp/en *(from 2004 -)* | |
| Full citation | |
| Form filled by | Date and name |
| Author contact information | |
| Other publications on same trial | |

Eligibility

| | |
|---|---|
| Confirm eligibility | Yes No Awaiting assessment |

Correspondence

| | |
|---|---|
| Correspondence required | Data for each intervention period |

Method

| | |
|---|---|
| Cluster-randomised | Yes/No<br>Intervention (number (n)) =, control (n) = |
| Location (e.g. hospital, out-clinic) | |
| Ethics approval | Yes/No/No information |
| Summary (method) | Cross-over trial with 2 interventions:<br>1. Methylphenidate<br>2. Control<br>Phases |

## Participants

| | |
|---|---|
| Summary (participants) | Number of participants screened |
| | Number of participants included |
| | Participants were randomly assigned to 1 of X possible drug condition orders |
| | Number of participants followed up |
| | Number of withdrawals |
| | *Diagnostic and Statistical Manual of Mental Disorders* (DSM) or *International Classification of Diseases* (ICD) diagnosis of ADHD (combined (%), hyperactive-impulsive (%), inattentive (%)) |
| | Age (years) (mean, range) |
| | IQ (mean, range) |
| | Sex (male, female) |
| | Methylphenidate naive (%/number) |
| | Ethnicity (Caucasian (%), African-american (%), Asian (%), Hispanic (%), other (%)) |
| | Country |
| | Comorbidity (type %) |
| | Comedication (no/yes) |
| | Sociodemographics (e.g. double- or single-parent family, low, middle or upper class) |
| | Inclusion criteria |
| | Exclusion criteria |

## Interventions

Participants were randomly assigned to 1 of X possible drug condition orders of methylphenidate and control
Methylphenidate dosage: Mean (standard deviation (SD))
Administration schedule: time points
Duration of each medication condition
Washout before trial initiation
Medication-free period between interventions
Titration period: none/duration initiated before/after randomisation
Treatment compliance

## Outcome listing

(Our outcomes according to our protocol: short, general description)

ADHD symptoms

Measure instrument (e.g. ADHD Rating Scale (ADHD-RS), Swanson, Kotkin, Atkins, M-Flynn and Pelham (SKAMP) scale), parent-/teacher-/independent assessor-rated, time point

General behaviour

Measure instrument (e.g. Child Behavior Checklist (CBCL)), parent-/teacher-/independent assessor-rated, time point

Quality of life

Measure instrument, parent-/teacher-/independent assessor-rated, time point

Serious adverse events

Type of outcome/adverse event, measure method/instrument, parent- /teacher-/independent assessor-rated, time point

Non-serious adverse events

Type of outcome/adverse event, measure method/instrument, parent- /teacher-/independent assessor-rated, time point

**Outcomes (positive effects)**

*e.g. copy of table from article*

**Outcomes (adverse events)**

*e.g. copy of table from article*

| Outcomes specified | Types of adverse events/responses | Total numbers | Mean | SD | Time point |
|---|---|---|---|---|---|
| Serious adverse events (temporal association, but not necessarily causal relationship) | | | | | |
| Serious adverse reaction (response to the drug) | | | | | |
| Non-serious adverse events (temporal association) | | | | | |

Risk of bias

| Item | Quote | Risk of bias (high, unclear, low) |
|---|---|---|
| Random sequence generation/generation of allocation sequence (selection bias) | | |
| Allocation concealment (selection bias) | | |
| Blinding of participants and personnel (performance bias) | | |
| Blinding of outcome assessment (detection bias) | | |
| Incomplete outcome data (intention-to-treat (ITT), imputation method) (attrition bias)<br>Exclusion of placebo responders etc.: methylphenidate non-responders (after randomisation) | | |
| Selective outcome reporting (according to protocol?) | | |
| Vested interest | | |
| Other sources of bias | Authors' affiliations (e.g. Novartis)<br>Selection bias (e.g. titration after randomisation → exclusion of methylphenidate non-responders or placebo responders) | |

Notes

Sample calculation

Ethics approval

Comments from trial authors

Key conclusions of trial authors

Comments from review authors

Inclusion of methylphenidate responders only/exclusion of methylphenidate non-responders/children who have previously experienced adverse events while taking methylphenidate

Any withdrawals due to adverse events

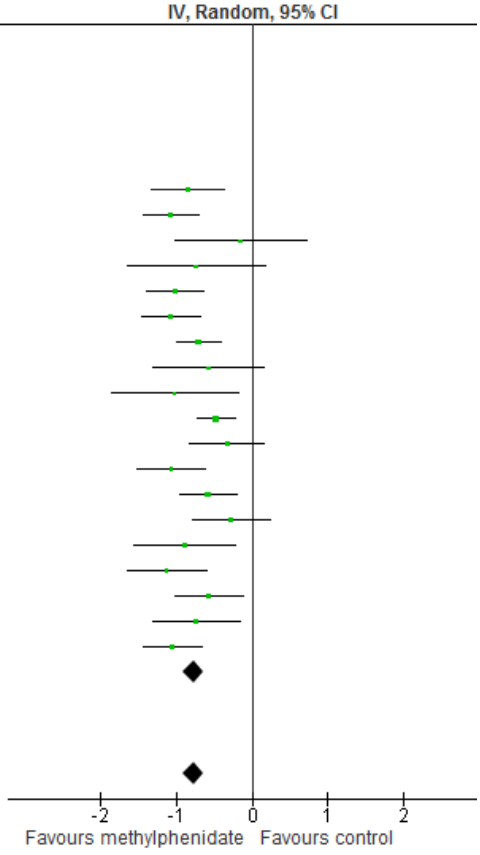
Supplemental information/data received through personal email correspondence with trial authors in *month* 2014

# Graphs

## 1 - Teacher-rated ADHD symptoms

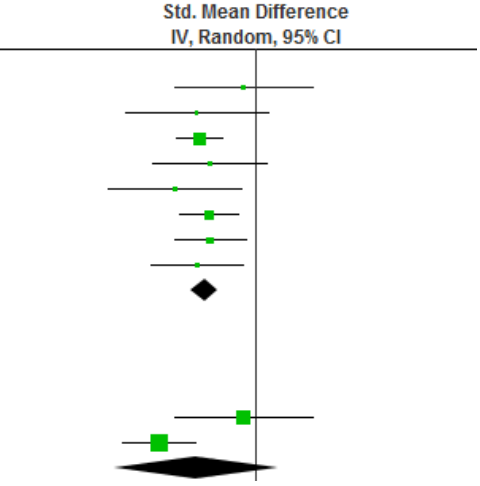
**1.1 All parallel-group trials and first-period cross-over trials**

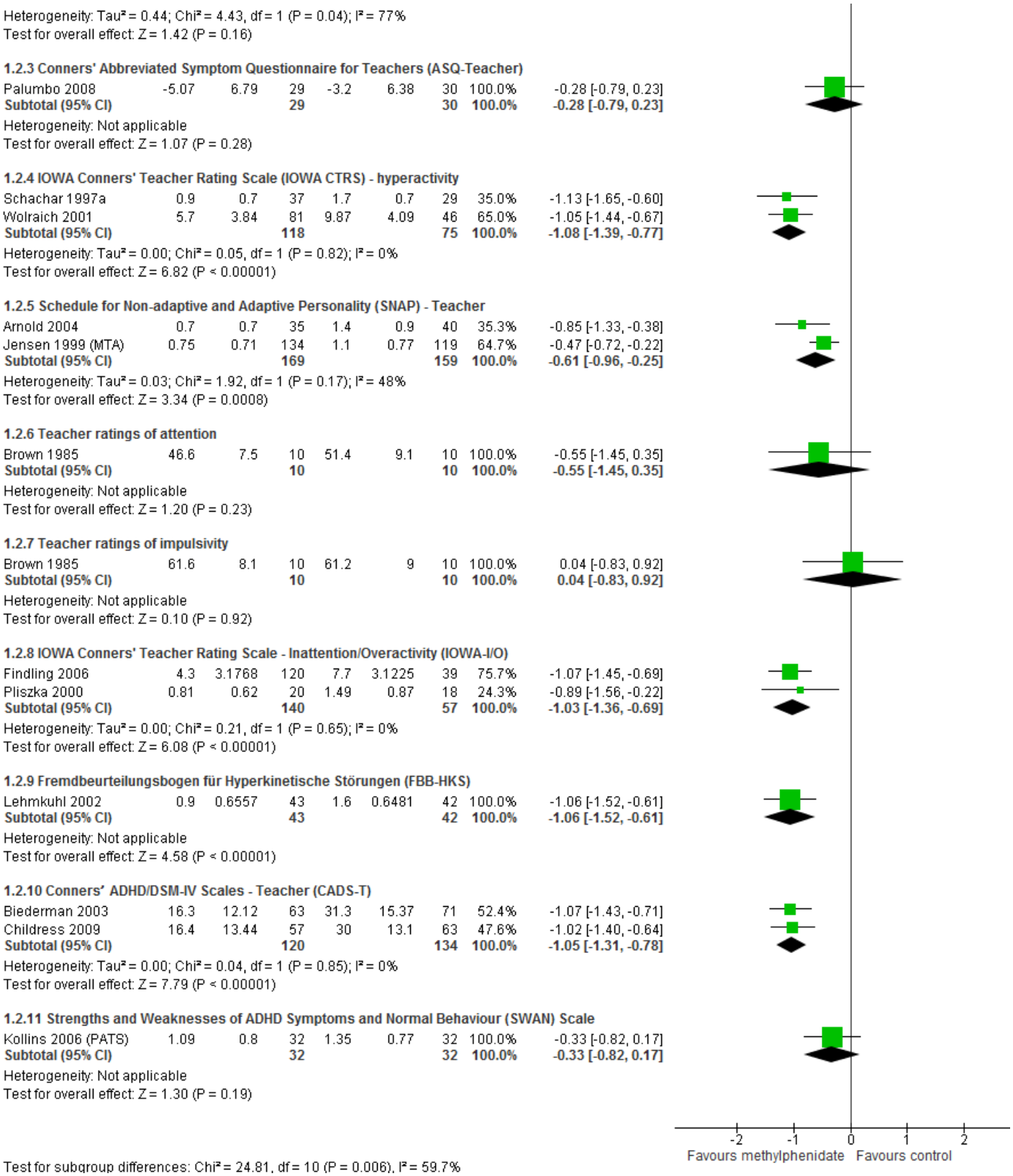
| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.1.1 Low risk of bias** | | | | | | | | |
| **Subtotal (95% CI)** | | | **0** | | | **0** | | **Not estimable** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | | |
| **1.1.2 High risk of bias** | | | | | | | | |
| Arnold 2004 | 0.7 | 0.7 | 35 | 1.4 | 0.9 | 40 | 5.3% | -0.85 [-1.33, -0.38] |
| Biederman 2003 | 16.3 | 12.12 | 63 | 31.3 | 15.37 | 71 | 7.2% | -1.07 [-1.43, -0.71] |
| Brown 1985 | 15.1 | 4.6 | 10 | 15.7 | 2.9 | 10 | 2.0% | -0.15 [-1.03, 0.73] |
| Butter 1983 | 30.47 | 17.3 | 10 | 42.7 | 14.2 | 10 | 1.9% | -0.74 [-1.65, 0.17] |
| Childress 2009 | 16.4 | 13.44 | 57 | 30 | 13.1 | 63 | 6.8% | -1.02 [-1.40, -0.64] |
| Findling 2006 | 4.3 | 3.1768 | 120 | 7.7 | 3.1225 | 39 | 6.9% | -1.07 [-1.45, -0.69] |
| Findling 2008 | 18.3 | 17.44 | 94 | 31.6 | 20.07 | 88 | 8.7% | -0.71 [-1.01, -0.41] |
| Firestone 1981 | 8.9 | 4.93 | 18 | 11.77 | 4.83 | 13 | 2.8% | -0.57 [-1.30, 0.16] |
| Ialongo 1994 | 7.53 | 7.41 | 13 | 15.25 | 7.27 | 12 | 2.2% | -1.02 [-1.86, -0.17] |
| Jensen 1999 (MTA) | 0.75 | 0.71 | 134 | 1.1 | 0.77 | 119 | 10.0% | -0.47 [-0.72, -0.22] |
| Kollins 2006 (PATS) | 1.09 | 0.8 | 32 | 1.35 | 0.77 | 32 | 5.0% | -0.33 [-0.82, 0.17] |
| Lehmkuhl 2002 | 0.9 | 0.6557 | 43 | 1.6 | 0.6481 | 42 | 5.5% | -1.06 [-1.52, -0.61] |
| Moshe 2012 | 58 | 10.3 | 57 | 64.7 | 12.5 | 57 | 7.0% | -0.58 [-0.96, -0.21] |
| Palumbo 2008 | -5.07 | 6.79 | 29 | -3.2 | 6.38 | 30 | 4.7% | -0.28 [-0.79, 0.23] |
| Pliszka 2000 | 0.81 | 0.62 | 20 | 1.49 | 0.87 | 18 | 3.2% | -0.89 [-1.56, -0.22] |
| Schachar 1997a | 0.9 | 0.7 | 37 | 1.7 | 0.7 | 29 | 4.6% | -1.13 [-1.65, -0.60] |
| Taylor 1987 | 0.54 | 1.04 | 39 | 1.22 | 1.3 | 39 | 5.6% | -0.57 [-1.03, -0.12] |
| Van der Meere 1999a | 73.6 | 12.7133 | 24 | 83.1 | 12.7133 | 24 | 3.9% | -0.73 [-1.32, -0.15] |
| Wolraich 2001 | 5.7 | 3.84 | 81 | 9.87 | 4.09 | 46 | 6.8% | -1.05 [-1.44, -0.67] |
| **Subtotal (95% CI)** | | | **916** | | | **782** | **100.0%** | **-0.77 [-0.90, -0.64]** |
| Heterogeneity: Tau² = 0.03; Chi² = 28.78, df = 18 (P = 0.05); I² = 37% | | | | | | | | |
| Test for overall effect: Z = 11.23 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **916** | | | **782** | **100.0%** | **-0.77 [-0.90, -0.64]** |
| Heterogeneity: Tau² = 0.03; Chi² = 28.78, df = 18 (P = 0.05); I² = 37% | | | | | | | | |
| Test for overall effect: Z = 11.23 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | |




**1.2 Subgroup analysis: types of scales**

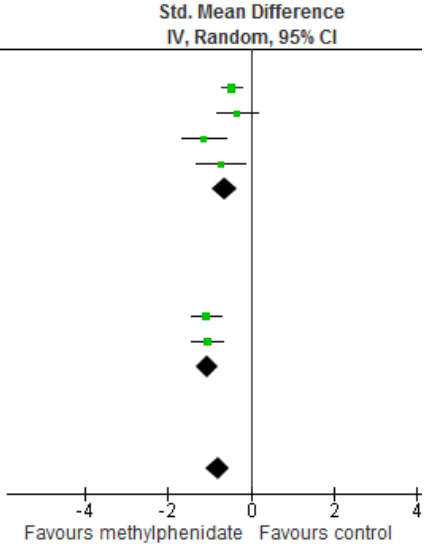
| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.2.1 Conners' Teacher Rating Scale (CTRS)** | | | | | | | | |
| Brown 1985 | 15.1 | 4.6 | 10 | 15.7 | 2.9 | 10 | 4.1% | -0.15 [-1.03, 0.73] |
| Butter 1983 | 30.47 | 17.3 | 10 | 42.7 | 14.2 | 10 | 3.8% | -0.74 [-1.65, 0.17] |
| Findling 2008 | 18.3 | 17.44 | 94 | 31.6 | 20.07 | 88 | 35.0% | -0.71 [-1.01, -0.41] |
| Firestone 1981 | 8.9 | 4.93 | 18 | 11.77 | 4.83 | 13 | 5.9% | -0.57 [-1.30, 0.16] |
| Ialongo 1994 | 7.53 | 7.41 | 13 | 15.25 | 7.27 | 12 | 4.4% | -1.02 [-1.86, -0.17] |
| Moshe 2012 | 58 | 10.3 | 57 | 64.7 | 12.5 | 57 | 22.4% | -0.58 [-0.96, -0.21] |
| Taylor 1987 | 0.54 | 1.04 | 39 | 1.22 | 1.3 | 39 | 15.3% | -0.57 [-1.03, -0.12] |
| Van der Meere 1999a | 73.6 | 12.7133 | 24 | 83.1 | 12.7133 | 24 | 9.2% | -0.73 [-1.32, -0.15] |
| **Subtotal (95% CI)** | | | **265** | | | **253** | **100.0%** | **-0.64 [-0.82, -0.47]** |
| Heterogeneity: Tau² = 0.00; Chi² = 2.51, df = 7 (P = 0.93); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 7.12 (P < 0.00001) | | | | | | | | |
| **1.2.2 Abbreviated Conners' Rating Scale (ACRS) - Teacher** | | | | | | | | |
| Brown 1985 | 15.1 | 4.6 | 10 | 15.7 | 2.9 | 10 | 43.6% | -0.15 [-1.03, 0.73] |
| Lehmkuhl 2002 | 7 | 6.5574 | 43 | 15 | 6.4807 | 42 | 56.4% | -1.22 [-1.68, -0.75] |
| **Subtotal (95% CI)** | | | **53** | | | **52** | **100.0%** | **-0.75 [-1.79, 0.29]** |




Heterogeneity: Tau² = 0.44; Chi² = 4.43, df = 1 (P = 0.04); I² = 77%
Test for overall effect: Z = 1.42 (P = 0.16)
1.2.3 Conners' Abbreviated Symptom Questionnaire for Teachers (ASQ-Teacher)
Palumbo 2008 -5.07 6.79 29 -3.2 6.38 30 100.0% -0.28 [-0.79, 0.23]
Subtotal (95% CI) 29 30 100.0% -0.28 [-0.79, 0.23]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.07 (P = 0.28)
1.2.4 IOWA Conners' Teacher Rating Scale (IOWA CTRS) - hyperactivity
Schachar 1997a 0.9 0.7 37 1.7 0.7 29 35.0% -1.13 [-1.65, -0.60]
Wolraich 2001 5.7 3.84 81 9.87 4.09 46 65.0% -1.05 [-1.44, -0.67]
Subtotal (95% CI) 118 75 100.0% -1.08 [-1.39, -0.77]
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 6.82 (P < 0.00001)
1.2.5 Schedule for Non-adaptive and Adaptive Personality (SNAP) - Teacher
Arnold 2004 0.7 0.7 35 1.4 0.9 40 35.3% -0.85 [-1.33, -0.38]
Jensen 1999 (MTA) 0.75 0.71 134 1.1 0.77 119 64.7% -0.47 [-0.72, -0.22]
Subtotal (95% CI) 169 159 100.0% -0.61 [-0.96, -0.25]
Heterogeneity: Tau² = 0.03; Chi² = 1.92, df = 1 (P = 0.17); I² = 48%
Test for overall effect: Z = 3.34 (P = 0.0008)
1.2.6 Teacher ratings of attention
Brown 1985 46.6 7.5 10 51.4 9.1 10 100.0% -0.55 [-1.45, 0.35]
Subtotal (95% CI) 10 10 100.0% -0.55 [-1.45, 0.35]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.20 (P = 0.23)
1.2.7 Teacher ratings of impulsivity
Brown 1985 61.6 8.1 10 61.2 9 10 100.0% 0.04 [-0.83, 0.92]
Subtotal (95% CI) 10 10 100.0% 0.04 [-0.83, 0.92]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.10 (P = 0.92)
1.2.8 IOWA Conners' Teacher Rating Scale - Inattention/Overactivity (IOWA-I/O)
Findling 2006 4.3 3.1768 120 7.7 3.1225 39 75.7% -1.07 [-1.45, -0.69]
Pliszka 2000 0.81 0.62 20 1.49 0.87 18 24.3% -0.89 [-1.56, -0.22]
Subtotal (95% CI) 140 57 100.0% -1.03 [-1.36, -0.69]
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 6.08 (P < 0.00001)
1.2.9 Fremdbeurteilungsbogen für Hyperkinetische Störungen (FBB-HKS)
Lehmkuhl 2002 0.9 0.6557 43 1.6 0.6481 42 100.0% -1.06 [-1.52, -0.61]
Subtotal (95% CI) 43 42 100.0% -1.06 [-1.52, -0.61]
Heterogeneity: Not applicable
Test for overall effect: Z = 4.58 (P < 0.00001)
1.2.10 Conners' ADHD/DSM-IV Scales - Teacher (CADS-T)
Biederman 2003 16.3 12.12 63 31.3 15.37 71 52.4% -1.07 [-1.43, -0.71]
Childress 2009 16.4 13.44 57 30 13.1 63 47.6% -1.02 [-1.40, -0.64]
Subtotal (95% CI) 120 134 100.0% -1.05 [-1.31, -0.78]
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%
Test for overall effect: Z = 7.79 (P < 0.00001)
1.2.11 Strengths and Weaknesses of ADHD Symptoms and Normal Behaviour (SWAN) Scale
Kollins 2006 (PATS) 1.09 0.8 32 1.35 0.77 32 100.0% -0.33 [-0.82, 0.17]
Subtotal (95% CI) 32 32 100.0% -0.33 [-0.82, 0.17]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.30 (P = 0.19)
-2
-1
0
1
2
Favours methylphenidate
Favours control
Test for subgroup differences: Chi² = 24.81, df = 10 (P = 0.006), I² = 59.7%

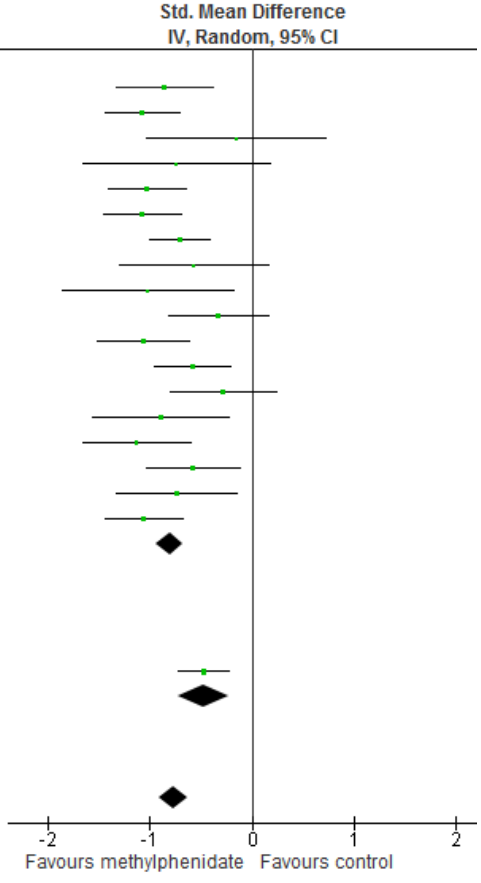
**1.3 Medication status: medication naive versus not medication naive**

| Study or Subgroup | Favours methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.3.1 Medication naive** | | | | | | | | |
| Jensen 1999 (MTA) | 0.75 | 0.71 | 134 | 1.1 | 0.77 | 119 | 22.1% | -0.47 [-0.72, -0.22] |
| Kollins 2006 (PATS) | 1.09 | 0.8 | 32 | 1.35 | 0.77 | 32 | 14.9% | -0.33 [-0.82, 0.17] |
| Schachar 1997a | 0.9 | 0.7 | 37 | 1.7 | 0.7 | 29 | 14.1% | -1.13 [-1.65, -0.60] |
| Van der Meere 1999a | 73.6 | 12.7133 | 24 | 83.1 | 12.7133 | 24 | 12.7% | -0.73 [-1.32, -0.15] |
| **Subtotal (95% CI)** | | | **227** | | | **204** | **63.8%** | **-0.63 [-0.94, -0.31]** |
| Heterogeneity: Tau² = 0.05; Chi² = 6.18, df = 3 (P = 0.10); I² = 51% | | | | | | | | |
| Test for overall effect: Z = 3.86 (P = 0.0001) | | | | | | | | |
| **1.3.2 Not medication naive** | | | | | | | | |
| Findling 2006 | 4.3 | 3.1768 | 120 | 7.7 | 3.1225 | 39 | 18.2% | -1.07 [-1.45, -0.69] |
| Wolraich 2001 | 5.7 | 3.84 | 81 | 9.87 | 4.09 | 46 | 18.0% | -1.05 [-1.44, -0.67] |
| **Subtotal (95% CI)** | | | **201** | | | **85** | **36.2%** | **-1.06 [-1.33, -0.79]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 7.69 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **428** | | | **289** | **100.0%** | **-0.79 [-1.08, -0.50]** |
| Heterogeneity: Tau² = 0.08; Chi² = 14.63, df = 5 (P = 0.01); I² = 66% | | | | | | | | |
| Test for overall effect: Z = 5.36 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 4.18, df = 1 (P = 0.04), I² = 76.1% | | | | | | | | |

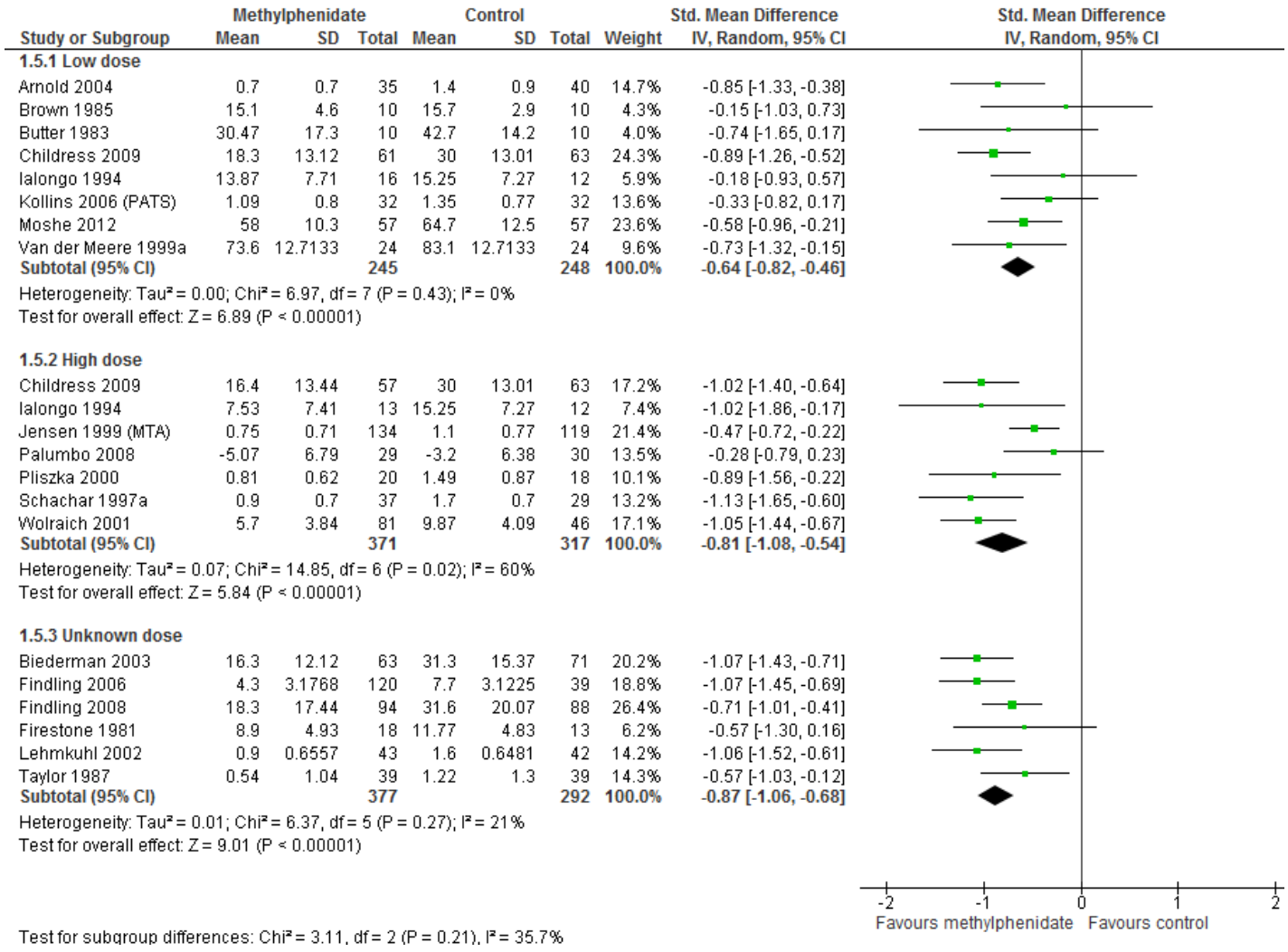



**1.4 Subgroup analysis: duration of treatment**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.4.1 Short term (up to 6 months)** | | | | | | | | |
| Arnold 2004 | 0.7 | 0.7 | 35 | 1.4 | 0.9 | 40 | 5.3% | -0.85 [-1.33, -0.38] |
| Biederman 2003 | 16.3 | 12.12 | 63 | 31.3 | 15.37 | 71 | 7.2% | -1.07 [-1.43, -0.71] |
| Brown 1985 | 15.1 | 4.6 | 10 | 15.7 | 2.9 | 10 | 2.0% | -0.15 [-1.03, 0.73] |
| Butter 1983 | 30.47 | 17.3 | 10 | 42.7 | 14.2 | 10 | 1.9% | -0.74 [-1.65, 0.17] |
| Childress 2009 | 16.4 | 13.44 | 57 | 30 | 13.01 | 63 | 6.8% | -1.02 [-1.40, -0.64] |
| Findling 2006 | 4.3 | 3.1768 | 120 | 7.7 | 3.1225 | 39 | 6.9% | -1.07 [-1.45, -0.69] |
| Findling 2008 | 18.3 | 17.44 | 94 | 31.6 | 20.07 | 88 | 8.7% | -0.71 [-1.01, -0.41] |
| Firestone 1981 | 8.9 | 4.93 | 18 | 11.77 | 4.83 | 13 | 2.8% | -0.57 [-1.30, 0.16] |
| Ialongo 1994 | 7.53 | 7.41 | 13 | 15.25 | 7.27 | 12 | 2.2% | -1.02 [-1.86, -0.17] |
| Kollins 2006 (PATS) | 1.09 | 0.8 | 32 | 1.35 | 0.77 | 32 | 5.0% | -0.33 [-0.82, 0.17] |
| Lehmkuhl 2002 | 0.9 | 0.6557 | 43 | 1.6 | 0.6481 | 42 | 5.5% | -1.06 [-1.52, -0.61] |
| Moshe 2012 | 58 | 10.3 | 57 | 64.7 | 12.5 | 57 | 7.0% | -0.58 [-0.96, -0.21] |
| Palumbo 2008 | -5.07 | 6.79 | 29 | -3.2 | 6.38 | 30 | 4.7% | -0.28 [-0.79, 0.23] |
| Pliszka 2000 | 0.81 | 0.62 | 20 | 1.49 | 0.87 | 18 | 3.2% | -0.89 [-1.56, -0.22] |
| Schachar 1997a | 0.9 | 0.7 | 37 | 1.7 | 0.7 | 29 | 4.6% | -1.13 [-1.65, -0.60] |
| Taylor 1987 | 0.54 | 1.04 | 39 | 1.22 | 1.3 | 39 | 5.6% | -0.57 [-1.03, -0.12] |
| Van der Meere 1999a | 73.6 | 12.7133 | 24 | 83.1 | 12.7133 | 24 | 3.9% | -0.73 [-1.32, -0.15] |
| Wolraich 2001 | 5.7 | 3.84 | 81 | 9.87 | 4.09 | 46 | 6.8% | -1.05 [-1.44, -0.67] |
| **Subtotal (95% CI)** | | | **782** | | | **663** | **90.0%** | **-0.81 [-0.94, -0.68]** |
| Heterogeneity: Tau² = 0.02; Chi² = 22.81, df = 17 (P = 0.16); I² = 25% | | | | | | | | |
| Test for overall effect: Z = 12.02 (P < 0.00001) | | | | | | | | |
| **1.4.2 Long term (over 6 months)** | | | | | | | | |
| Jensen 1999 (MTA) | 0.75 | 0.71 | 134 | 1.1 | 0.77 | 119 | 10.0% | -0.47 [-0.72, -0.22] |
| **Subtotal (95% CI)** | | | **134** | | | **119** | **10.0%** | **-0.47 [-0.72, -0.22]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 3.70 (P = 0.0002) | | | | | | | | |
| **Total (95% CI)** | | | **916** | | | **782** | **100.0%** | **-0.77 [-0.90, -0.64]** |
| Heterogeneity: Tau² = 0.03; Chi² = 28.82, df = 18 (P = 0.05); I² = 38% | | | | | | | | |
| Test for overall effect: Z = 11.22 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 5.37, df = 1 (P = 0.02), I² = 81.4% | | | | | | | | |

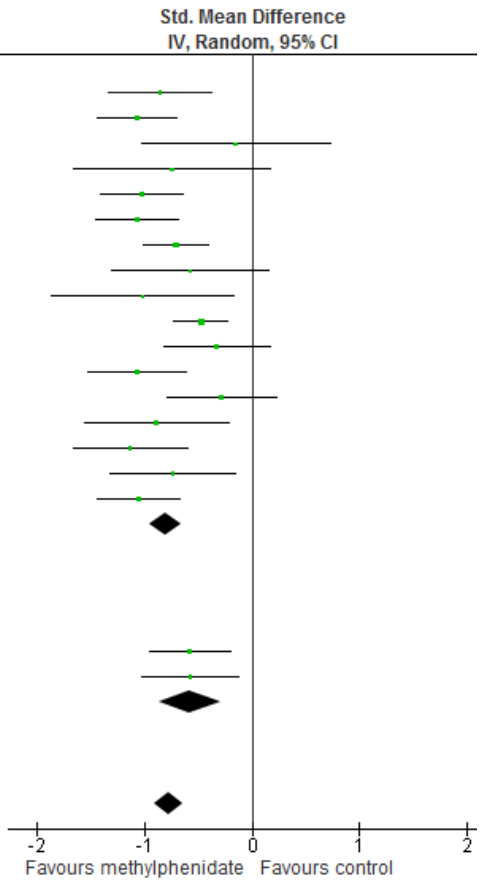


**1.5 Subgroup analysis: dose**



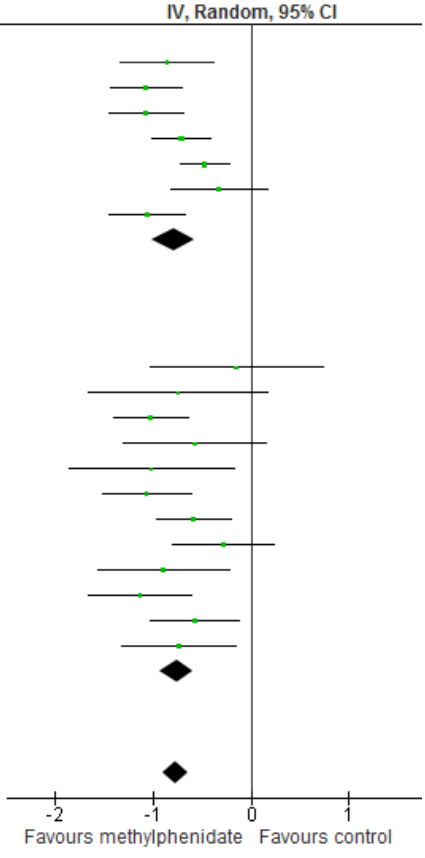
**1.6 Subgroup analysis: parallel-group trials compared with first-period cross-over trials**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.6.1 Parallel-group trials** | | | | | | | | |
| Arnold 2004 | 0.7 | 0.7 | 35 | 1.4 | 0.9 | 40 | 5.3% | -0.85 [-1.33, -0.38] |
| Biederman 2003 | 16.3 | 12.12 | 63 | 31.3 | 15.37 | 71 | 7.2% | -1.07 [-1.43, -0.71] |
| Brown 1985 | 15.1 | 4.6 | 10 | 15.7 | 2.9 | 10 | 2.0% | -0.15 [-1.03, 0.73] |
| Butter 1983 | 30.47 | 17.3 | 10 | 42.7 | 14.2 | 10 | 1.9% | -0.74 [-1.65, 0.17] |
| Childress 2009 | 16.4 | 13.44 | 57 | 30 | 13.01 | 63 | 6.8% | -1.02 [-1.40, -0.64] |
| Findling 2006 | 4.3 | 3.1768 | 120 | 7.7 | 3.1225 | 39 | 6.9% | -1.07 [-1.45, -0.69] |
| Findling 2008 | 18.3 | 17.44 | 94 | 31.6 | 20.07 | 88 | 8.7% | -0.71 [-1.01, -0.41] |
| Firestone 1981 | 8.9 | 4.93 | 18 | 11.77 | 4.83 | 13 | 2.8% | -0.57 [-1.30, 0.16] |
| Ialongo 1994 | 7.53 | 7.41 | 13 | 15.25 | 7.27 | 12 | 2.2% | -1.02 [-1.86, -0.17] |
| Jensen 1999 (MTA) | 0.75 | 0.71 | 134 | 1.1 | 0.77 | 119 | 10.0% | -0.47 [-0.72, -0.22] |
| Kollins 2006 (PATS) | 1.09 | 0.8 | 32 | 1.35 | 0.77 | 32 | 5.0% | -0.33 [-0.82, 0.17] |
| Lehmkuhl 2002 | 0.9 | 0.6557 | 43 | 1.6 | 0.6481 | 42 | 5.5% | -1.06 [-1.52, -0.61] |
| Palumbo 2008 | -5.07 | 6.79 | 29 | -3.2 | 6.38 | 30 | 4.7% | -0.28 [-0.79, 0.23] |
| Pliszka 2000 | 0.81 | 0.62 | 20 | 1.49 | 0.87 | 18 | 3.2% | -0.89 [-1.56, -0.22] |
| Schachar 1997a | 0.9 | 0.7 | 37 | 1.7 | 0.7 | 29 | 4.6% | -1.13 [-1.65, -0.60] |
| Van der Meere 1999a | 73.6 | 12.7133 | 24 | 83.1 | 12.7133 | 24 | 3.9% | -0.73 [-1.32, -0.15] |
| Wolraich 2001 | 5.7 | 3.84 | 81 | 9.87 | 4.09 | 46 | 6.8% | -1.05 [-1.44, -0.67] |
| **Subtotal (95% CI)** | | | **820** | | | **686** | **87.4%** | **-0.80 [-0.95, -0.65]** |
| Heterogeneity: Tau² = 0.04; Chi² = 27.09, df = 16 (P = 0.04); I² = 41% | | | | | | | | |
| Test for overall effect: Z = 10.49 (P < 0.00001) | | | | | | | | |
| **1.6.2 First-period cross-over trials** | | | | | | | | |
| Moshe 2012 | 58 | 10.3 | 57 | 64.7 | 12.5 | 57 | 7.0% | -0.58 [-0.96, -0.21] |
| Taylor 1987 | 0.54 | 1.04 | 39 | 1.22 | 1.3 | 39 | 5.6% | -0.57 [-1.03, -0.12] |
| **Subtotal (95% CI)** | | | **96** | | | **96** | **12.6%** | **-0.58 [-0.87, -0.29]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 3.92 (P < 0.0001) | | | | | | | | |
| **Total (95% CI)** | | | **916** | | | **782** | **100.0%** | **-0.77 [-0.90, -0.64]** |
| Heterogeneity: Tau² = 0.03; Chi² = 28.82, df = 18 (P = 0.05); I² = 38% | | | | | | | | |
| Test for overall effect: Z = 11.22 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 1.77, df = 1 (P = 0.18), I² = 43.4% | | | | | | | | |



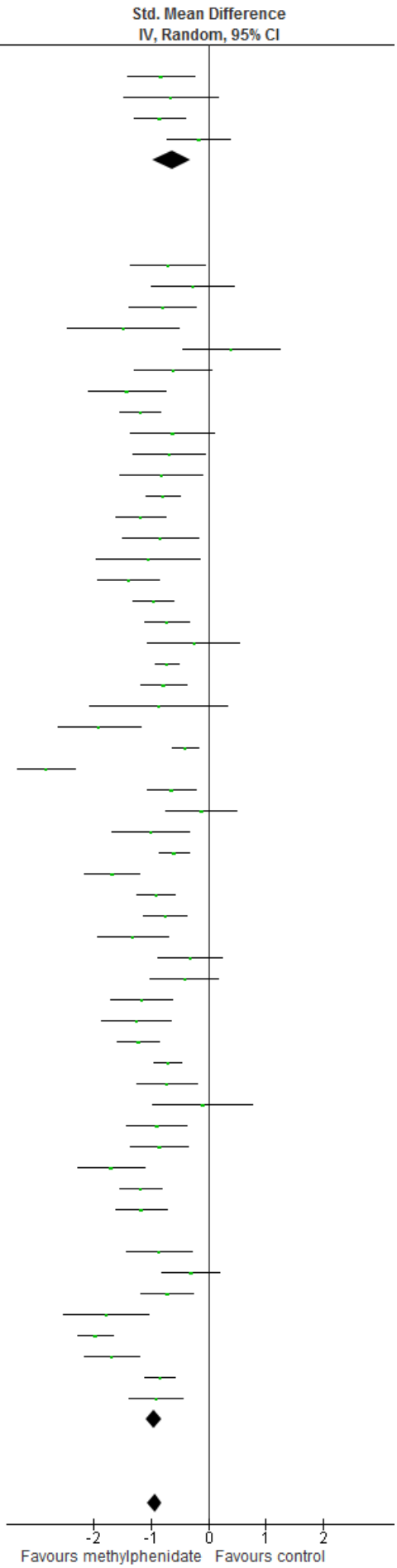

**1.7 Subgroup analysis: trials with cohort selection bias of all participants compared with trials without cohort selection bias of all participants**

| Study or Subgroup | Favours methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.7.1 Trials with cohort selection bias of all participants** | | | | | | | | |
| Arnold 2004 | 0.7 | 0.7 | 35 | 1.4 | 0.9 | 40 | 5.3% | -0.85 [-1.33, -0.38] |
| Biederman 2003 | 16.3 | 12.12 | 63 | 31.3 | 15.37 | 71 | 7.2% | -1.07 [-1.43, -0.71] |
| Findling 2006 | 4.3 | 3.1768 | 120 | 7.7 | 3.1225 | 39 | 6.9% | -1.07 [-1.45, -0.69] |
| Findling 2008 | 18.3 | 17.44 | 94 | 31.6 | 20.07 | 88 | 8.7% | -0.71 [-1.01, -0.41] |
| Jensen 1999 (MTA) | 0.75 | 0.71 | 134 | 1.1 | 0.77 | 119 | 10.0% | -0.47 [-0.72, -0.22] |
| Kollins 2006 (PATS) | 1.09 | 0.8 | 32 | 1.35 | 0.77 | 32 | 5.0% | -0.33 [-0.82, 0.17] |
| Wolraich 2001 | 5.7 | 3.84 | 81 | 9.87 | 4.09 | 46 | 6.8% | -1.05 [-1.44, -0.67] |
| **Subtotal (95% CI)** | | | **559** | | | **435** | **49.8%** | **-0.79 [-1.01, -0.57]** |
| Heterogeneity: Tau² = 0.05; Chi² = 15.88, df = 6 (P = 0.01); I² = 62% | | | | | | | | |
| Test for overall effect: Z = 6.93 (P < 0.00001) | | | | | | | | |
| **1.7.2 Trials without cohort selection bias of all participants** | | | | | | | | |
| Brown 1985 | 15.1 | 4.6 | 10 | 15.7 | 2.9 | 10 | 2.0% | -0.15 [-1.03, 0.73] |
| Butter 1983 | 30.47 | 17.3 | 10 | 42.7 | 14.2 | 10 | 1.9% | -0.74 [-1.65, 0.17] |
| Childress 2009 | 16.4 | 13.44 | 57 | 30 | 13.01 | 63 | 6.8% | -1.02 [-1.40, -0.64] |
| Firestone 1981 | 8.9 | 4.93 | 18 | 11.77 | 4.83 | 13 | 2.8% | -0.57 [-1.30, 0.16] |
| Ialongo 1994 | 7.53 | 7.41 | 13 | 15.25 | 7.27 | 12 | 2.2% | -1.02 [-1.86, -0.17] |
| Lehmkuhl 2002 | 0.9 | 0.6557 | 43 | 1.6 | 0.6481 | 42 | 5.5% | -1.06 [-1.52, -0.61] |
| Moshe 2012 | 58 | 10.3 | 57 | 64.7 | 12.5 | 57 | 7.0% | -0.58 [-0.96, -0.21] |
| Palumbo 2008 | -5.07 | 6.79 | 29 | -3.2 | 6.38 | 30 | 4.7% | -0.28 [-0.79, 0.23] |
| Pliszka 2000 | 0.81 | 0.62 | 20 | 1.49 | 0.87 | 18 | 3.2% | -0.89 [-1.56, -0.22] |
| Schachar 1997a | 0.9 | 0.7 | 37 | 1.7 | 0.7 | 29 | 4.6% | -1.13 [-1.65, -0.60] |
| Taylor 1987 | 0.54 | 1.04 | 39 | 1.22 | 1.3 | 39 | 5.6% | -0.57 [-1.03, -0.12] |
| Van der Meere 1999a | 73.6 | 12.7133 | 24 | 83.1 | 12.7133 | 24 | 3.9% | -0.73 [-1.32, -0.15] |
| **Subtotal (95% CI)** | | | **357** | | | **347** | **50.2%** | **-0.76 [-0.93, -0.59]** |
| Heterogeneity: Tau² = 0.01; Chi² = 12.94, df = 11 (P = 0.30); I² = 15% | | | | | | | | |
| Test for overall effect: Z = 8.66 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **916** | | | **782** | **100.0%** | **-0.77 [-0.90, -0.64]** |
| Heterogeneity: Tau² = 0.03; Chi² = 28.82, df = 18 (P = 0.05); I² = 38% | | | | | | | | |
| Test for overall effect: Z = 11.22 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0% | | | | | | | | |

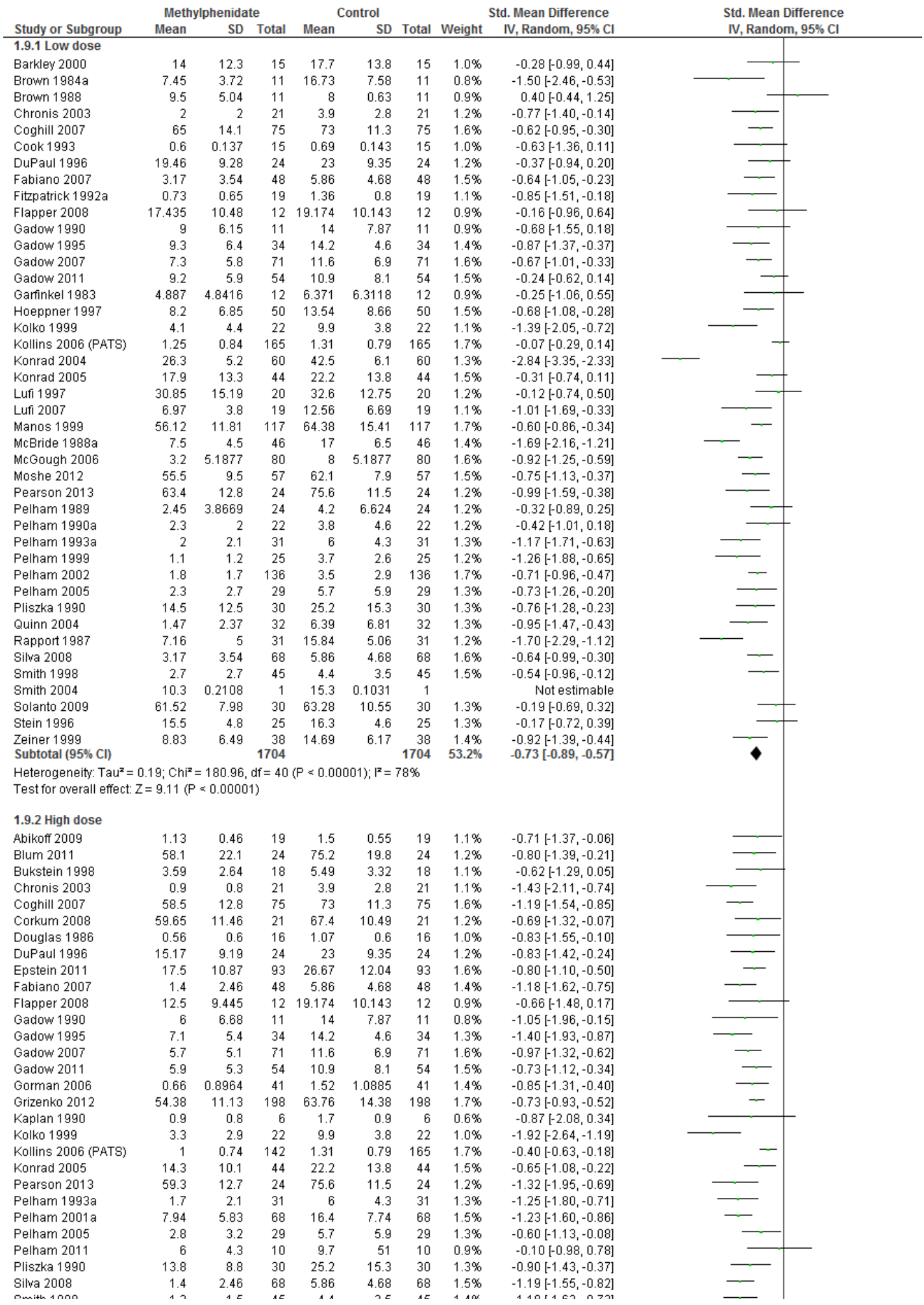


**1.8 ADHD symptoms, cross-over trial (endpoint data)**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.8.1 Low risk of bias** | | | | | | | | |
| DuPaul 1996 | 15.17 | 9.19 | 24 | 23 | 9.35 | 24 | 1.6% | -0.83 [-1.42, -0.24] |
| Flapper 2008 | 12.5 | 9.445 | 12 | 19.174 | 10.143 | 12 | 1.2% | -0.66 [-1.48, 0.17] |
| Gorman 2006 | 0.66 | 0.8964 | 41 | 1.52 | 1.0885 | 41 | 1.9% | -0.85 [-1.31, -0.40] |
| Stein 1996 | 15.5 | 4.8 | 25 | 16.3 | 4.6 | 25 | 1.7% | -0.17 [-0.72, 0.39] |
| **Subtotal (95% CI)** | | | **102** | | | **102** | **6.5%** | **-0.64 [-0.97, -0.30]** |
| Heterogeneity: Tau² = 0.03; Chi² = 4.04, df = 3 (P = 0.26); I² = 26% | | | | | | | | |
| Test for overall effect: Z = 3.72 (P = 0.0002) | | | | | | | | |
| **1.8.2 High risk of bias** | | | | | | | | |
| Abikoff 2009 | 1.13 | 0.46 | 19 | 1.5 | 0.55 | 19 | 1.5% | -0.71 [-1.37, -0.06] |
| Barkley 2000 | 14 | 12.3 | 15 | 17.7 | 13.8 | 15 | 1.4% | -0.28 [-0.99, 0.44] |
| Blum 2011 | 58.1 | 22.1 | 24 | 75.2 | 19.8 | 24 | 1.6% | -0.80 [-1.39, -0.21] |
| Brown 1984a | 7.45 | 3.72 | 11 | 16.73 | 7.58 | 11 | 1.0% | -1.50 [-2.46, -0.53] |
| Brown 1988 | 10 | 6.69 | 11 | 8 | 0.63 | 11 | 1.2% | 0.40 [-0.44, 1.25] |
| Bukstein 1998 | 3.59 | 2.64 | 18 | 5.49 | 3.32 | 18 | 1.5% | -0.62 [-1.29, 0.05] |
| Chronis 2003 | 0.9 | 0.8 | 21 | 3.9 | 2.8 | 21 | 1.5% | -1.43 [-2.11, -0.74] |
| Coghill 2007 | 58.5 | 12.8 | 75 | 73 | 11.3 | 75 | 2.1% | -1.19 [-1.54, -0.85] |
| Cook 1993 | 0.6 | 0.137 | 15 | 0.69 | 0.143 | 15 | 1.4% | -0.63 [-1.36, 0.11] |
| Corkum 2008 | 59.65 | 11.46 | 21 | 67.4 | 10.49 | 21 | 1.6% | -0.69 [-1.32, -0.07] |
| Douglas 1986 | 0.56 | 0.6 | 16 | 1.07 | 0.6 | 16 | 1.4% | -0.83 [-1.55, -0.10] |
| Epstein 2011 | 17.5 | 10.87 | 93 | 26.67 | 12.04 | 93 | 2.2% | -0.80 [-1.10, -0.50] |
| Fabiano 2007 | 1.4 | 2.46 | 48 | 5.86 | 4.68 | 48 | 1.9% | -1.18 [-1.62, -0.75] |
| Fitzpatrick 1992a | 0.73 | 0.65 | 19 | 1.36 | 0.8 | 19 | 1.5% | -0.85 [-1.51, -0.18] |
| Gadow 1990 | 6 | 6.68 | 11 | 14 | 7.87 | 11 | 1.1% | -1.05 [-1.96, -0.15] |
| Gadow 1995 | 7.1 | 5.4 | 34 | 14.2 | 4.6 | 34 | 1.7% | -1.40 [-1.93, -0.87] |
| Gadow 2007 | 5.7 | 5.1 | 71 | 11.6 | 6.9 | 71 | 2.1% | -0.97 [-1.32, -0.62] |
| Gadow 2011 | 5.9 | 5.3 | 54 | 10.9 | 8.1 | 54 | 2.0% | -0.73 [-1.12, -0.34] |
| Garfinkel 1983 | 4.887 | 4.8416 | 12 | 6.371 | 6.3118 | 12 | 1.3% | -0.25 [-1.06, 0.55] |
| Grizenko 2012 | 54.38 | 11.13 | 198 | 63.76 | 14.38 | 198 | 2.4% | -0.73 [-0.93, -0.52] |
| Hoeppner 1997 | 8.2 | 6.85 | 50 | 14.23 | 8.31 | 50 | 2.0% | -0.79 [-1.19, -0.38] |
| Kaplan 1990 | 0.9 | 0.8 | 6 | 1.7 | 0.9 | 6 | 0.8% | -0.87 [-2.08, 0.34] |
| Kolko 1999 | 3.3 | 2.9 | 22 | 9.9 | 3.8 | 22 | 1.4% | -1.92 [-2.64, -1.19] |
| Kollins 2006 (PATS) | 1 | 0.74 | 142 | 1.31 | 0.79 | 165 | 2.3% | -0.40 [-0.63, -0.18] |
| Konrad 2004 | 26.3 | 5.2 | 60 | 42.5 | 6.1 | 60 | 1.8% | -2.84 [-3.35, -2.33] |
| Konrad 2005 | 14.3 | 10.1 | 44 | 22.2 | 13.8 | 44 | 2.0% | -0.65 [-1.08, -0.22] |
| Lufi 1997 | 30.85 | 15.19 | 20 | 32.6 | 12.75 | 20 | 1.6% | -0.12 [-0.74, 0.50] |
| Lufi 2007 | 6.97 | 3.8 | 19 | 12.56 | 6.69 | 19 | 1.5% | -1.01 [-1.69, -0.33] |
| Manos 1999 | 56.12 | 11.81 | 117 | 64.38 | 15.41 | 117 | 2.3% | -0.60 [-0.86, -0.34] |
| McBride 1988a | 7.5 | 4.5 | 46 | 17 | 6.5 | 46 | 1.9% | -1.69 [-2.16, -1.21] |
| McGough 2006 | 3.2 | 5.1877 | 80 | 8 | 5.1877 | 80 | 2.2% | -0.92 [-1.25, -0.59] |
| Moshe 2012 | 55.5 | 9.5 | 57 | 62.1 | 7.9 | 57 | 2.1% | -0.75 [-1.13, -0.37] |
| Pearson 2013 | 59.3 | 12.7 | 24 | 75.6 | 11.5 | 24 | 1.6% | -1.32 [-1.95, -0.69] |
| Pelham 1989 | 2.45 | 3.8669 | 24 | 4.2 | 6.624 | 24 | 1.7% | -0.32 [-0.89, 0.25] |
| Pelham 1990a | 2.3 | 2 | 22 | 3.8 | 4.6 | 22 | 1.6% | -0.42 [-1.01, 0.18] |
| Pelham 1993a | 2 | 2.1 | 31 | 6 | 4.3 | 31 | 1.7% | -1.17 [-1.71, -0.63] |
| Pelham 1999 | 1.1 | 1.2 | 25 | 3.7 | 2.6 | 25 | 1.6% | -1.26 [-1.88, -0.65] |
| Pelham 2001a | 7.94 | 5.83 | 68 | 16.4 | 7.74 | 68 | 2.1% | -1.23 [-1.60, -0.86] |
| Pelham 2002 | 1.8 | 1.7 | 136 | 3.5 | 2.9 | 136 | 2.3% | -0.71 [-0.96, -0.47] |
| Pelham 2005 | 2.3 | 2.7 | 29 | 5.7 | 5.9 | 29 | 1.7% | -0.73 [-1.26, -0.20] |
| Pelham 2011 | 6 | 4.3 | 10 | 9.7 | 51 | 10 | 1.2% | -0.10 [-0.98, 0.78] |
| Pliszka 1990 | 13.8 | 8.8 | 30 | 25.2 | 15.3 | 30 | 1.7% | -0.90 [-1.43, -0.37] |
| Quinn 2004 | 1.58 | 3.85 | 32 | 6.39 | 6.81 | 32 | 1.8% | -0.86 [-1.37, -0.35] |
| Rapport 1987 | 7.16 | 5 | 31 | 15.84 | 5.06 | 31 | 1.6% | -1.70 [-2.29, -1.12] |
| Silva 2008 | 1.4 | 2.46 | 68 | 5.86 | 4.68 | 68 | 2.1% | -1.19 [-1.55, -0.82] |
| Smith 1998 | 1.2 | 1.5 | 45 | 4.4 | 3.5 | 45 | 1.9% | -1.18 [-1.63, -0.73] |
| Smith 2004 | 10.3 | 0.2108 | 1 | 15.3 | 0.1031 | 1 | | Not estimable |
| Smithee 1998 | 0.647 | 0.51 | 25 | 1.1249 | 0.5766 | 25 | 1.7% | -0.86 [-1.45, -0.28] |
| Solanto 2009 | 60.04 | 10.57 | 30 | 63.28 | 10.55 | 30 | 1.8% | -0.30 [-0.81, 0.21] |
| Taylor 1987 | 0.85 | 1 | 39 | 1.59 | 1.04 | 39 | 1.9% | -0.72 [-1.18, -0.26] |
| Tirosh 1993a | 17.6 | 6.3 | 20 | 32 | 9.2 | 20 | 1.4% | -1.79 [-2.53, -1.05] |
| Ullmann 1986 | -45.6 | 19.2 | 118 | -11.3 | 15.1 | 118 | 2.2% | -1.98 [-2.29, -1.67] |
| Wigal 2013 | 7.1 | 5.64 | 44 | 19.3 | 8.38 | 44 | 1.8% | -1.69 [-2.18, -1.20] |
| Wilens 2008 | 15.4 | 10.7354 | 120 | 24.5 | 10.7354 | 120 | 2.3% | -0.84 [-1.11, -0.58] |
| Zeiner 1999 | 8.83 | 6.49 | 38 | 14.69 | 6.17 | 38 | 1.9% | -0.92 [-1.39, -0.44] |
| **Subtotal (95% CI)** | | | **2459** | | | **2482** | **93.5%** | **-0.95 [-1.09, -0.82]** |
| Heterogeneity: Tau² = 0.17; Chi² = 235.24, df = 53 (P < 0.00001); I² = 77% | | | | | | | | |
| Test for overall effect: Z = 14.00 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **2561** | | | **2584** | **100.0%** | **-0.93 [-1.06, -0.80]** |
| Heterogeneity: Tau² = 0.17; Chi² = 242.57, df = 57 (P < 0.00001); I² = 77% | | | | | | | | |
| Test for overall effect: Z = 14.31 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 2.91, df = 1 (P = 0.09), I² = 65.7% | | | | | | | | |




**1.9 ADHD symptoms, cross-over trials (endpoint data), subgroup analysis: dose**

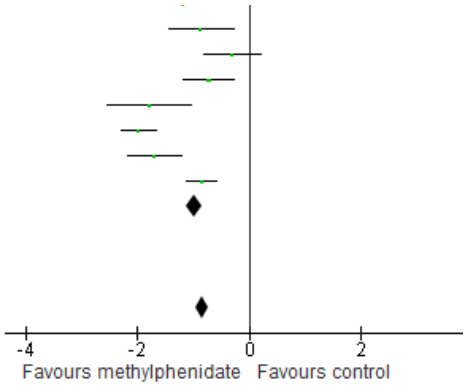

Methylphenidate
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
1.9.1 Low dose
Barkley 2000 14 12.3 15 17.7 13.8 15 1.0% -0.28 [-0.99, 0.44]
Brown 1984a 7.45 3.72 11 16.73 7.58 11 0.8% -1.50 [-2.46, -0.53]
Brown 1988 9.5 5.04 11 8 0.63 11 0.9% 0.40 [-0.44, 1.25]
Chronis 2003 2 2 21 3.9 2.8 21 1.2% -0.77 [-1.40, -0.14]
Coghill 2007 65 14.1 75 73 11.3 75 1.6% -0.62 [-0.95, -0.30]
Cook 1993 0.6 0.137 15 0.69 0.143 15 1.0% -0.63 [-1.36, 0.11]
DuPaul 1996 19.46 9.28 24 23 9.35 24 1.2% -0.37 [-0.94, 0.20]
Fabiano 2007 3.17 3.54 48 5.86 4.68 48 1.5% -0.64 [-1.05, -0.23]
Fitzpatrick 1992a 0.73 0.65 19 1.36 0.8 19 1.1% -0.85 [-1.51, -0.18]
Flapper 2008 17.435 10.48 12 19.174 10.143 12 0.9% -0.16 [-0.96, 0.64]
Gadow 1990 9 6.15 11 14 7.87 11 0.9% -0.68 [-1.55, 0.18]
Gadow 1995 9.3 6.4 34 14.2 4.6 34 1.4% -0.87 [-1.37, -0.37]
Gadow 2007 7.3 5.8 71 11.6 6.9 71 1.6% -0.67 [-1.01, -0.33]
Gadow 2011 9.2 5.9 54 10.9 8.1 54 1.5% -0.24 [-0.62, 0.14]
Garfinkel 1983 4.887 4.8416 12 6.371 6.3118 12 0.9% -0.25 [-1.06, 0.55]
Hoeppner 1997 8.2 6.85 50 13.54 8.66 50 1.5% -0.68 [-1.08, -0.28]
Kolko 1999 4.1 4.4 22 9.9 3.8 22 1.1% -1.39 [-2.05, -0.72]
Kollins 2006 (PATS) 1.25 0.84 165 1.31 0.79 165 1.7% -0.07 [-0.29, 0.14]
Konrad 2004 26.3 5.2 60 42.5 6.1 60 1.3% -2.84 [-3.35, -2.33]
Konrad 2005 17.9 13.3 44 22.2 13.8 44 1.5% -0.31 [-0.74, 0.11]
Lufi 1997 30.85 15.19 20 32.6 12.75 20 1.2% -0.12 [-0.74, 0.50]
Lufi 2007 6.97 3.8 19 12.56 6.69 19 1.1% -1.01 [-1.69, -0.33]
Manos 1999 56.12 11.81 117 64.38 15.41 117 1.7% -0.60 [-0.86, -0.34]
McBride 1988a 7.5 4.5 46 17 6.5 46 1.4% -1.69 [-2.16, -1.21]
McGough 2006 3.2 5.1877 80 8 5.1877 80 1.6% -0.92 [-1.25, -0.59]
Moshe 2012 55.5 9.5 57 62.1 7.9 57 1.5% -0.75 [-1.13, -0.37]
Pearson 2013 63.4 12.8 24 75.6 11.5 24 1.2% -0.99 [-1.59, -0.38]
Pelham 1989 2.45 3.8669 24 4.2 6.624 24 1.2% -0.32 [-0.89, 0.25]
Pelham 1990a 2.3 2 22 3.8 4.6 22 1.2% -0.42 [-1.01, 0.18]
Pelham 1993a 2 2.1 31 6 4.3 31 1.3% -1.17 [-1.71, -0.63]
Pelham 1999 1.1 1.2 25 3.7 2.6 25 1.2% -1.26 [-1.88, -0.65]
Pelham 2002 1.8 1.7 136 3.5 2.9 136 1.7% -0.71 [-0.96, -0.47]
Pelham 2005 2.3 2.7 29 5.7 5.9 29 1.3% -0.73 [-1.26, -0.20]
Pliszka 1990 14.5 12.5 30 25.2 15.3 30 1.3% -0.76 [-1.28, -0.23]
Quinn 2004 1.47 2.37 32 6.39 6.81 32 1.3% -0.95 [-1.47, -0.43]
Rapport 1987 7.16 5 31 15.84 5.06 31 1.2% -1.70 [-2.29, -1.12]
Silva 2008 3.17 3.54 68 5.86 4.68 68 1.6% -0.64 [-0.99, -0.30]
Smith 1998 2.7 2.7 45 4.4 3.5 45 1.5% -0.54 [-0.96, -0.12]
Smith 2004 10.3 0.2108 1 15.3 0.1031 1 Not estimable
Solanto 2009 61.52 7.98 30 63.28 10.55 30 1.3% -0.19 [-0.69, 0.32]
Stein 1996 15.5 4.8 25 16.3 4.6 25 1.3% -0.17 [-0.72, 0.39]
Zeiner 1999 8.83 6.49 38 14.69 6.17 38 1.4% -0.92 [-1.39, -0.44]
Subtotal (95% CI) 1704 1704 53.2% -0.73 [-0.89, -0.57]
Heterogeneity: Tau² = 0.19; Chi² = 180.96, df = 40 (P < 0.00001); I² = 78%
Test for overall effect: Z = 9.11 (P < 0.00001)
1.9.2 High dose
Abikoff 2009 1.13 0.46 19 1.5 0.55 19 1.1% -0.71 [-1.37, -0.06]
Blum 2011 58.1 22.1 24 75.2 19.8 24 1.2% -0.80 [-1.39, -0.21]
Bukstein 1998 3.59 2.64 18 5.49 3.32 18 1.1% -0.62 [-1.29, 0.05]
Chronis 2003 0.9 0.8 21 3.9 2.8 21 1.1% -1.43 [-2.11, -0.74]
Coghill 2007 58.5 12.8 75 73 11.3 75 1.6% -1.19 [-1.54, -0.85]
Corkum 2008 59.65 11.46 21 67.4 10.49 21 1.2% -0.69 [-1.32, -0.07]
Douglas 1986 0.56 0.6 16 1.07 0.6 16 1.0% -0.83 [-1.55, -0.10]
DuPaul 1996 15.17 9.19 24 23 9.35 24 1.2% -0.83 [-1.42, -0.24]
Epstein 2011 17.5 10.87 93 26.67 12.04 93 1.6% -0.80 [-1.10, -0.50]
Fabiano 2007 1.4 2.46 48 5.86 4.68 48 1.4% -1.18 [-1.62, -0.75]
Flapper 2008 12.5 9.445 12 19.174 10.143 12 0.9% -0.66 [-1.48, 0.17]
Gadow 1990 6 6.68 11 14 7.87 11 0.8% -1.05 [-1.96, -0.15]
Gadow 1995 7.1 5.4 34 14.2 4.6 34 1.3% -1.40 [-1.93, -0.87]
Gadow 2007 5.7 5.1 71 11.6 6.9 71 1.6% -0.97 [-1.32, -0.62]
Gadow 2011 5.9 5.3 54 10.9 8.1 54 1.5% -0.73 [-1.12, -0.34]
Gorman 2006 0.66 0.8964 41 1.52 1.0885 41 1.4% -0.85 [-1.31, -0.40]
Grizenko 2012 54.38 11.13 198 63.76 14.38 198 1.7% -0.73 [-0.93, -0.52]
Kaplan 1990 0.9 0.8 6 1.7 0.9 6 0.6% -0.87 [-2.08, 0.34]
Kolko 1999 3.3 2.9 22 9.9 3.8 22 1.0% -1.92 [-2.64, -1.19]
Kollins 2006 (PATS) 1 0.74 142 1.31 0.79 165 1.7% -0.40 [-0.63, -0.18]
Konrad 2005 14.3 10.1 44 22.2 13.8 44 1.5% -0.65 [-1.08, -0.22]
Pearson 2013 59.3 12.7 24 75.6 11.5 24 1.2% -1.32 [-1.95, -0.69]
Pelham 1993a 1.7 2.1 31 6 4.3 31 1.3% -1.25 [-1.80, -0.71]
Pelham 2001a 7.94 5.83 68 16.4 7.74 68 1.5% -1.23 [-1.60, -0.86]
Pelham 2005 2.8 3.2 29 5.7 5.9 29 1.3% -0.60 [-1.13, -0.08]
Pelham 2011 6 4.3 10 9.7 51 10 0.9% -0.10 [-0.98, 0.78]
Pliszka 1990 13.8 8.8 30 25.2 15.3 30 1.3% -0.90 [-1.43, -0.37]
Silva 2008 1.4 2.46 68 5.86 4.68 68 1.5% -1.19 [-1.55, -0.82]

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Smith 1998 | 1.2 | 1.5 | 45 | 4.4 | 3.5 | 45 | 1.4% | -1.18 [-1.63, -0.73] |
| Smithee 1998 | 0.647 | 0.51 | 25 | 1.1249 | 0.5766 | 25 | 1.2% | -0.86 [-1.45, -0.28] |
| Solanto 2009 | 60.04 | 10.57 | 30 | 63.28 | 10.55 | 30 | 1.3% | -0.30 [-0.81, 0.21] |
| Taylor 1987 | 0.85 | 1 | 39 | 1.59 | 1.04 | 39 | 1.4% | -0.72 [-1.18, -0.26] |
| Tirosh 1993a | 17.6 | 6.3 | 20 | 32 | 9.2 | 20 | 1.0% | -1.79 [-2.53, -1.05] |
| Ullmann 1986 | -45.6 | 19.2 | 118 | -11.3 | 15.1 | 118 | 1.6% | -1.98 [-2.29, -1.67] |
| Wigal 2013 | 7.1 | 5.64 | 44 | 19.3 | 8.38 | 44 | 1.4% | -1.69 [-2.18, -1.20] |
| Wilens 2008 | 15.4 | 10.7354 | 120 | 24.5 | 10.7354 | 120 | 1.7% | -0.84 [-1.11, -0.58] |
| **Subtotal (95% CI)** | | | **1695** | | | **1718** | **46.8%** | **-0.98 [-1.13, -0.84]** |

Heterogeneity: Tau² = 0.13; Chi² = 124.79, df = 35 (P < 0.00001); I² = 72%
Test for overall effect: Z = 13.24 (P < 0.00001)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Total (95% CI)** | | | **3399** | | | **3422** | **100.0%** | **-0.85 [-0.96, -0.74]** |

Heterogeneity: Tau² = 0.17; Chi² = 333.89, df = 76 (P < 0.00001); I² = 77%
Test for overall effect: Z = 14.98 (P < 0.00001)
Test for subgroup differences: Chi² = 5.30, df = 1 (P = 0.02), I² = 81.1%

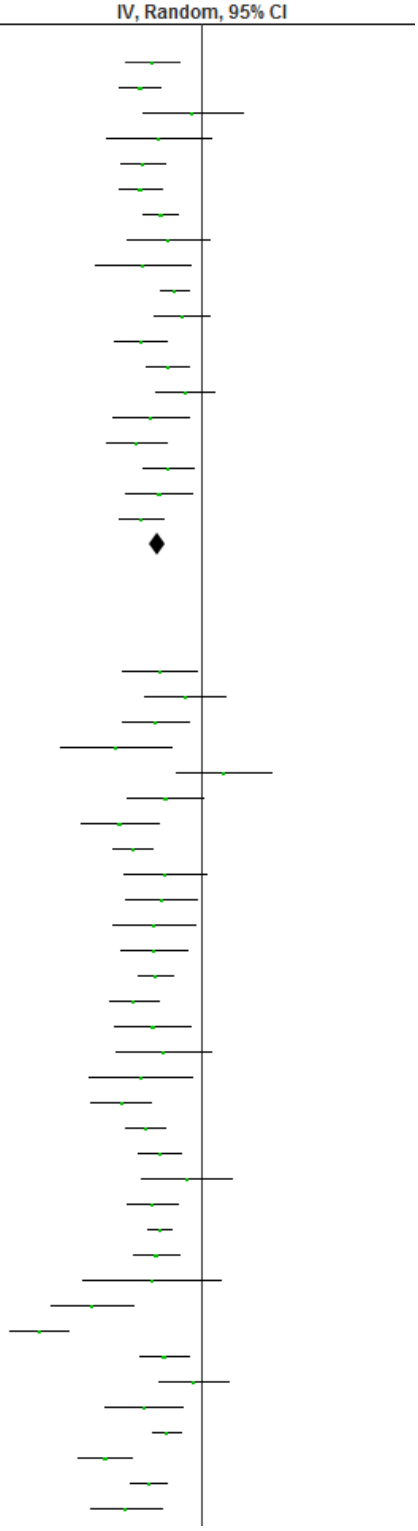



**1.10 Subgroup analysis: all parallel-group trials and first-period cross-over trials compared with cross-over trials (endpoint data)**

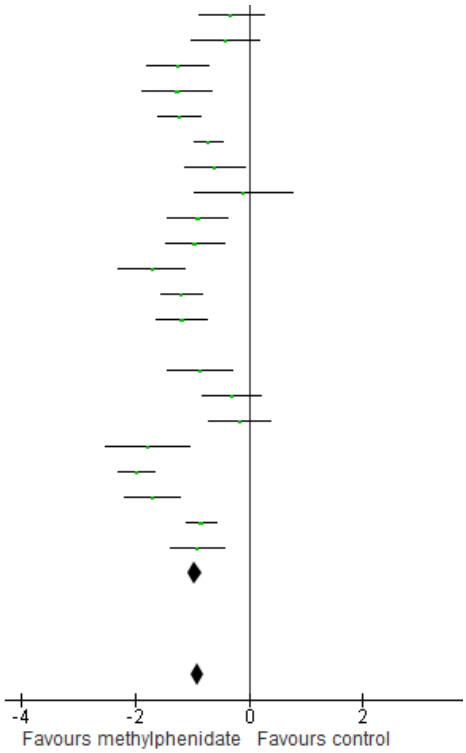
| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.10.1 All parallel-group trials and first-period cross-over trials** | | | | | | | | |
| Arnold 2004 | 0.7 | 0.7 | 35 | 1.4 | 0.9 | 40 | 1.5% | -0.85 [-1.33, -0.38] |
| Biederman 2003 | 16.3 | 12.12 | 63 | 31.3 | 15.37 | 71 | 1.7% | -1.07 [-1.43, -0.71] |
| Brown 1985 | 15.1 | 4.6 | 10 | 15.7 | 2.9 | 10 | 0.9% | -0.15 [-1.03, 0.73] |
| Butter 1983 | 30.47 | 17.3 | 10 | 42.7 | 14.2 | 10 | 0.8% | -0.74 [-1.65, 0.17] |
| Childress 2009 | 16.4 | 13.44 | 57 | 30 | 13.01 | 63 | 1.6% | -1.02 [-1.40, -0.64] |
| Findling 2006 | 4.3 | 3.1768 | 120 | 7.7 | 3.1225 | 39 | 1.6% | -1.07 [-1.45, -0.69] |
| Findling 2008 | 18.3 | 17.44 | 94 | 31.6 | 20.07 | 88 | 1.8% | -0.71 [-1.01, -0.41] |
| Firestone 1981 | 8.9 | 4.93 | 18 | 11.77 | 4.83 | 13 | 1.0% | -0.57 [-1.30, 0.16] |
| Ialongo 1994 | 7.53 | 7.41 | 13 | 15.25 | 7.27 | 12 | 0.9% | -1.02 [-1.86, -0.17] |
| Jensen 1999 (MTA) | 0.75 | 0.71 | 134 | 1.1 | 0.77 | 119 | 1.9% | -0.47 [-0.72, -0.22] |
| Kollins 2006 (PATS) | 1.09 | 0.8 | 32 | 1.35 | 0.77 | 32 | 1.4% | -0.33 [-0.82, 0.17] |
| Lehmkuhl 2002 | 0.9 | 0.6557 | 43 | 1.6 | 0.6481 | 42 | 1.5% | -1.06 [-1.52, -0.61] |
| Moshe 2012 | 58 | 10.3 | 57 | 64.7 | 12.5 | 57 | 1.7% | -0.58 [-0.96, -0.21] |
| Palumbo 2008 | -5.07 | 6.79 | 29 | -3.2 | 6.38 | 30 | 1.4% | -0.28 [-0.79, 0.23] |
| Pliszka 2000 | 0.81 | 0.62 | 20 | 1.49 | 0.87 | 18 | 1.1% | -0.89 [-1.56, -0.22] |
| Schachar 1997a | 0.9 | 0.7 | 37 | 1.7 | 0.7 | 29 | 1.4% | -1.13 [-1.65, -0.60] |
| Taylor 1987 | 0.54 | 1.04 | 39 | 1.22 | 1.3 | 39 | 1.5% | -0.57 [-1.03, -0.12] |
| Van der Meere 1999a | 73.6 | 12.7133 | 24 | 83.1 | 12.7133 | 24 | 1.3% | -0.73 [-1.32, -0.15] |
| Wolraich 2001 | 5.7 | 3.84 | 81 | 9.87 | 4.09 | 46 | 1.6% | -1.05 [-1.44, -0.67] |
| **Subtotal (95% CI)** | | | **916** | | | **782** | **26.6%** | **-0.77 [-0.90, -0.64]** |

Heterogeneity: Tau² = 0.03; Chi² = 28.82, df = 18 (P = 0.05); I² = 38%
Test for overall effect: Z = 11.22 (P < 0.00001)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **1.10.2 Cross-over trials (endpoint data)** | | | | | | | | |
| Abikoff 2009 | 1.13 | 0.46 | 19 | 1.5 | 0.55 | 19 | 1.2% | -0.71 [-1.37, -0.06] |
| Barkley 2000 | 14 | 12.3 | 15 | 17.7 | 13.8 | 15 | 1.1% | -0.28 [-0.99, 0.44] |
| Blum 2011 | 58.1 | 22.1 | 24 | 75.2 | 19.8 | 24 | 1.3% | -0.80 [-1.39, -0.21] |
| Brown 1984a | 7.45 | 3.72 | 11 | 16.73 | 7.58 | 11 | 0.8% | -1.50 [-2.46, -0.53] |
| Brown 1988 | 9.5 | 5.04 | 11 | 8 | 0.63 | 11 | 0.9% | 0.40 [-0.44, 1.25] |
| Bukstein 1998 | 3.59 | 2.64 | 18 | 5.49 | 3.32 | 18 | 1.1% | -0.62 [-1.29, 0.05] |
| Chronis 2003 | 0.9 | 0.8 | 21 | 3.9 | 2.8 | 21 | 1.1% | -1.43 [-2.11, -0.74] |
| Coghill 2007 | 58.5 | 12.8 | 75 | 73 | 11.3 | 75 | 1.7% | -1.19 [-1.54, -0.85] |
| Cook 1993 | 0.6 | 0.137 | 15 | 0.69 | 0.143 | 15 | 1.0% | -0.63 [-1.36, 0.11] |
| Corkum 2008 | 59.65 | 11.46 | 21 | 67.4 | 10.49 | 21 | 1.2% | -0.69 [-1.32, -0.07] |
| Douglas 1986 | 0.56 | 0.6 | 16 | 1.07 | 0.6 | 16 | 1.1% | -0.83 [-1.55, -0.10] |
| DuPaul 1996 | 15.17 | 9.19 | 24 | 23 | 9.35 | 24 | 1.3% | -0.83 [-1.42, -0.24] |
| Epstein 2011 | 17.5 | 10.87 | 93 | 26.67 | 12.04 | 93 | 1.8% | -0.80 [-1.10, -0.50] |
| Fabiano 2007 | 1.4 | 2.46 | 48 | 5.86 | 4.68 | 48 | 1.5% | -1.18 [-1.62, -0.75] |
| Fitzpatrick 1992a | 0.73 | 0.65 | 19 | 1.36 | 0.8 | 19 | 1.1% | -0.85 [-1.51, -0.18] |
| Flapper 2008 | 12.5 | 9.445 | 12 | 19.174 | 10.143 | 12 | 0.9% | -0.66 [-1.48, 0.17] |
| Gadow 1990 | 6 | 6.68 | 11 | 14 | 7.87 | 11 | 0.8% | -1.05 [-1.96, -0.15] |
| Gadow 1995 | 7.1 | 5.4 | 34 | 14.2 | 4.6 | 34 | 1.4% | -1.40 [-1.93, -0.87] |
| Gadow 2007 | 5.7 | 5.1 | 71 | 11.6 | 6.9 | 71 | 1.7% | -0.97 [-1.32, -0.62] |
| Gadow 2011 | 5.9 | 5.3 | 54 | 10.9 | 8.1 | 54 | 1.6% | -0.73 [-1.12, -0.34] |
| Garfinkel 1983 | 4.887 | 4.8416 | 12 | 6.371 | 6.3118 | 12 | 0.9% | -0.25 [-1.06, 0.55] |
| Gorman 2006 | 0.66 | 0.8964 | 41 | 1.52 | 1.0885 | 41 | 1.5% | -0.85 [-1.31, -0.40] |
| Grizenko 2012 | 54.38 | 11.13 | 198 | 63.76 | 14.38 | 198 | 1.9% | -0.73 [-0.93, -0.52] |
| Hoeppner 1997 | 8.2 | 6.85 | 50 | 14.23 | 8.31 | 50 | 1.6% | -0.79 [-1.19, -0.38] |
| Kaplan 1990 | 0.9 | 0.8 | 6 | 1.7 | 0.9 | 6 | 0.6% | -0.87 [-2.08, 0.34] |
| Kolko 1999 | 3.3 | 2.9 | 22 | 9.9 | 3.8 | 22 | 1.1% | -1.92 [-2.64, -1.19] |
| Konrad 2004 | 26.3 | 5.2 | 60 | 42.5 | 6.1 | 60 | 1.4% | -2.84 [-3.35, -2.33] |
| Konrad 2005 | 14.3 | 10.1 | 44 | 22.2 | 13.8 | 44 | 1.6% | -0.65 [-1.08, -0.22] |
| Lufi 1997 | 30.85 | 15.19 | 20 | 32.6 | 12.75 | 20 | 1.2% | -0.12 [-0.74, 0.50] |
| Lufi 2007 | 6.97 | 3.8 | 19 | 12.56 | 6.69 | 19 | 1.1% | -1.01 [-1.69, -0.33] |
| Manos 1999 | 56.12 | 11.81 | 117 | 64.38 | 15.41 | 117 | 1.9% | -0.60 [-0.86, -0.34] |
| McBride 1988a | 7.5 | 4.5 | 46 | 17 | 6.5 | 46 | 1.5% | -1.69 [-2.16, -1.21] |
| McGough 2006 | 3.2 | 5.1877 | 80 | 8 | 5.1877 | 80 | 1.7% | -0.92 [-1.25, -0.59] |
| Pearson 2013 | 59.3 | 12.7 | 24 | 75.6 | 11.5 | 24 | 1.2% | -1.32 [-1.95, -0.69] |

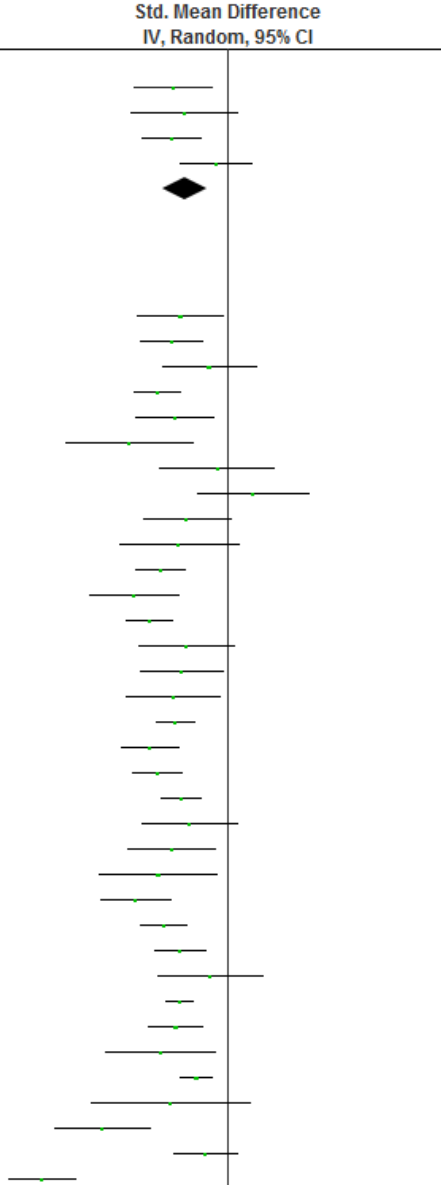


| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Pelham 1989 | 2.45 | 3.8669 | 24 | 4.2 | 6.624 | 24 | 1.3% | -0.32 [-0.89, 0.25] |
| Pelham 1990a | 2.3 | 2 | 22 | 3.8 | 4.6 | 22 | 1.3% | -0.42 [-1.01, 0.18] |
| Pelham 1993a | 1.7 | 2.1 | 31 | 6 | 4.3 | 31 | 1.3% | -1.25 [-1.80, -0.71] |
| Pelham 1999 | 1.1 | 1.2 | 25 | 3.7 | 2.6 | 25 | 1.2% | -1.26 [-1.88, -0.65] |
| Pelham 2001a | 7.94 | 5.83 | 68 | 16.4 | 7.74 | 68 | 1.7% | -1.23 [-1.60, -0.86] |
| Pelham 2002 | 1.8 | 1.7 | 136 | 3.5 | 2.9 | 136 | 1.9% | -0.71 [-0.96, -0.47] |
| Pelham 2005 | 2.8 | 3.2 | 29 | 5.7 | 5.9 | 29 | 1.4% | -0.60 [-1.13, -0.08] |
| Pelham 2011 | 6 | 4.3 | 10 | 9.7 | 51 | 10 | 0.9% | -0.10 [-0.98, 0.78] |
| Pliszka 1990 | 13.8 | 8.8 | 30 | 25.2 | 15.3 | 30 | 1.4% | -0.90 [-1.43, -0.37] |
| Quinn 2004 | 1.47 | 2.37 | 32 | 6.39 | 6.81 | 32 | 1.4% | -0.95 [-1.47, -0.43] |
| Rapport 1987 | 7.16 | 5 | 31 | 15.84 | 5.06 | 31 | 1.3% | -1.70 [-2.29, -1.12] |
| Silva 2008 | 1.4 | 2.46 | 68 | 5.86 | 4.68 | 68 | 1.7% | -1.19 [-1.55, -0.82] |
| Smith 1998 | 1.2 | 1.5 | 45 | 4.4 | 3.5 | 45 | 1.5% | -1.18 [-1.63, -0.73] |
| Smith 2004 | 10.3 | 0.2108 | 1 | 15.3 | 0.1031 | 1 | | Not estimable |
| Smithee 1998 | 0.647 | 0.51 | 25 | 1.1249 | 0.5766 | 25 | 1.3% | -0.86 [-1.45, -0.28] |
| Solanto 2009 | 60.04 | 10.57 | 30 | 63.28 | 10.55 | 30 | 1.4% | -0.30 [-0.81, 0.21] |
| Stein 1996 | 15.5 | 4.8 | 25 | 16.3 | 4.6 | 25 | 1.3% | -0.17 [-0.72, 0.39] |
| Tirosh 1993a | 17.6 | 6.3 | 20 | 32 | 9.2 | 20 | 1.0% | -1.79 [-2.53, -1.05] |
| Ullmann 1986 | -45.6 | 19.2 | 118 | -11.3 | 15.1 | 118 | 1.8% | -1.98 [-2.29, -1.67] |
| Wigal 2013 | 7.1 | 5.64 | 44 | 19.3 | 8.38 | 44 | 1.4% | -1.69 [-2.18, -1.20] |
| Wilens 2008 | 15.4 | 10.7354 | 120 | 24.5 | 10.7354 | 120 | 1.9% | -0.84 [-1.11, -0.58] |
| Zeiner 1999 | 8.83 | 6.49 | 38 | 14.69 | 6.17 | 38 | 1.5% | -0.92 [-1.39, -0.44] |
| **Subtotal (95% CI)** | | | **2323** | | | **2323** | **73.4%** | **-0.95 [-1.09, -0.82]** |
| Heterogeneity: Tau² = 0.17; Chi² = 222.00, df = 54 (P < 0.00001); I² = 76% | | | | | | | | |
| Test for overall effect: Z = 14.11 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **3239** | | | **3105** | **100.0%** | **-0.91 [-1.01, -0.80]** |
| Heterogeneity: Tau² = 0.14; Chi² = 260.75, df = 73 (P < 0.00001); I² = 72% | | | | | | | | |
| Test for overall effect: Z = 16.84 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 3.67, df = 1 (P = 0.06), I² = 72.8% | | | | | | | | |

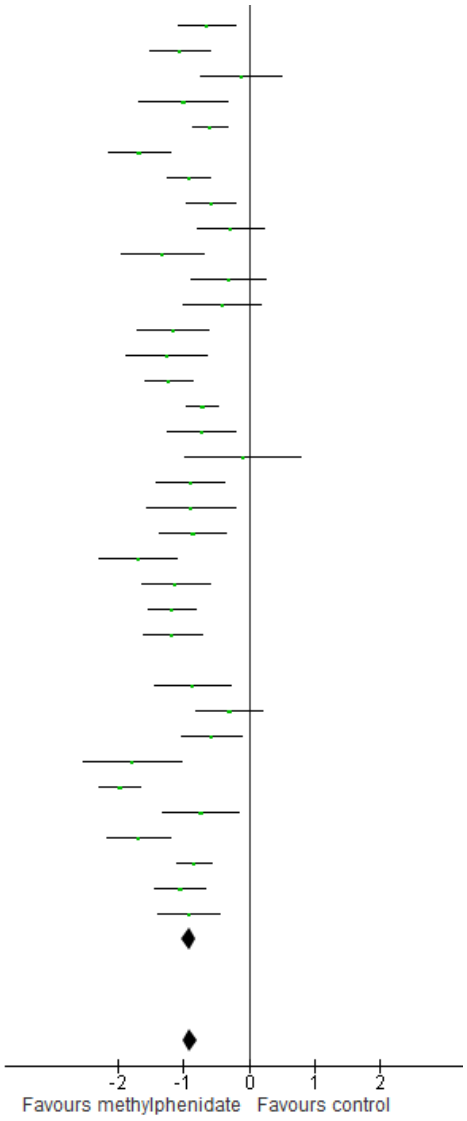



**1.11 All parallel-group trials and cross-over trials: risk of bias**

| | Methylphenidate | | | Control | | | | Std. Mean Difference |
|---|---|---|---|---|---|---|---|---|
| **Study or Subgroup** | **Mean** | **SD** | **Total** | **Mean** | **SD** | **Total** | **Weight** | **IV, Random, 95% CI** |
| **1.11.1 Low risk of bias** | | | | | | | | |
| DuPaul 1996 | 15.17 | 9.19 | 24 | 23 | 9.35 | 24 | 1.3% | -0.83 [-1.42, -0.24] |
| Flapper 2008 | 12.5 | 9.445 | 12 | 19.174 | 10.143 | 12 | 0.9% | -0.66 [-1.48, 0.17] |
| Gorman 2006 | 0.66 | 0.8964 | 41 | 1.52 | 1.0885 | 41 | 1.5% | -0.85 [-1.31, -0.40] |
| Stein 1996 | 15.5 | 4.8 | 25 | 16.3 | 4.6 | 25 | 1.3% | -0.17 [-0.72, 0.39] |
| **Subtotal (95% CI)** | | | **102** | | | **102** | **5.0%** | **-0.64 [-0.97, -0.30]** |
| Heterogeneity: Tau² = 0.03; Chi² = 4.04, df = 3 (P = 0.26); I² = 26% | | | | | | | | |
| Test for overall effect: Z = 3.72 (P = 0.0002) | | | | | | | | |
| **1.11.2 High risk of bias** | | | | | | | | |
| Abikoff 2009 | 1.13 | 0.46 | 19 | 1.5 | 0.55 | 19 | 1.2% | -0.71 [-1.37, -0.06] |
| Arnold 2004 | 0.7 | 0.7 | 35 | 1.4 | 0.9 | 40 | 1.5% | -0.85 [-1.33, -0.38] |
| Barkley 2000 | 14 | 12.3 | 15 | 17.7 | 13.8 | 15 | 1.1% | -0.28 [-0.99, 0.44] |
| Biederman 2003 | 16.3 | 12.12 | 63 | 31.3 | 15.37 | 71 | 1.7% | -1.07 [-1.43, -0.71] |
| Blum 2011 | 58.1 | 22.1 | 24 | 75.2 | 19.8 | 24 | 1.3% | -0.80 [-1.39, -0.21] |
| Brown 1984a | 7.45 | 3.72 | 11 | 16.73 | 7.58 | 11 | 0.8% | -1.50 [-2.46, -0.53] |
| Brown 1985 | 15.1 | 4.6 | 10 | 15.7 | 2.9 | 10 | 0.9% | -0.15 [-1.03, 0.73] |
| Brown 1988 | 10 | 6.69 | 11 | 8 | 0.63 | 11 | 0.9% | 0.40 [-0.44, 1.25] |
| Bukstein 1998 | 3.59 | 2.64 | 18 | 5.49 | 3.32 | 18 | 1.1% | -0.62 [-1.29, 0.05] |
| Butter 1983 | 30.47 | 17.3 | 10 | 42.7 | 14.2 | 10 | 0.8% | -0.74 [-1.65, 0.17] |
| Childress 2009 | 16.4 | 13.44 | 57 | 30 | 13.01 | 63 | 1.6% | -1.02 [-1.40, -0.64] |
| Chronis 2003 | 0.9 | 0.8 | 21 | 3.9 | 2.8 | 21 | 1.1% | -1.43 [-2.11, -0.74] |
| Coghill 2007 | 58.5 | 12.8 | 75 | 73 | 11.3 | 75 | 1.7% | -1.19 [-1.54, -0.85] |
| Cook 1993 | 0.6 | 0.137 | 15 | 0.69 | 0.143 | 15 | 1.0% | -0.63 [-1.36, 0.11] |
| Corkum 2008 | 59.65 | 11.46 | 21 | 67.4 | 10.49 | 21 | 1.2% | -0.69 [-1.32, -0.07] |
| Douglas 1986 | 0.56 | 0.6 | 16 | 1.07 | 0.6 | 16 | 1.0% | -0.83 [-1.55, -0.10] |
| Epstein 2011 | 17.5 | 10.87 | 93 | 26.67 | 12.04 | 93 | 1.8% | -0.80 [-1.10, -0.50] |
| Fabiano 2007 | 1.4 | 2.46 | 48 | 5.86 | 4.68 | 48 | 1.5% | -1.18 [-1.62, -0.75] |
| Findling 2006 | 4.3 | 3.1768 | 120 | 7.7 | 3.1225 | 39 | 1.6% | -1.07 [-1.45, -0.69] |
| Findling 2008 | 18.3 | 17.44 | 94 | 31.6 | 20.07 | 88 | 1.8% | -0.71 [-1.01, -0.41] |
| Firestone 1981 | 8.9 | 4.93 | 18 | 11.77 | 4.83 | 13 | 1.0% | -0.57 [-1.30, 0.16] |
| Fitzpatrick 1992a | 0.73 | 0.65 | 19 | 1.36 | 0.8 | 19 | 1.1% | -0.85 [-1.51, -0.18] |
| Gadow 1990 | 6 | 6.68 | 11 | 14 | 7.87 | 11 | 0.8% | -1.05 [-1.96, -0.15] |
| Gadow 1995 | 7.1 | 5.4 | 34 | 14.2 | 4.6 | 34 | 1.4% | -1.40 [-1.93, -0.87] |
| Gadow 2007 | 5.7 | 5.1 | 71 | 11.6 | 6.9 | 71 | 1.7% | -0.97 [-1.32, -0.62] |
| Gadow 2011 | 5.9 | 5.3 | 54 | 10.9 | 8.1 | 54 | 1.6% | -0.73 [-1.12, -0.34] |
| Garfinkel 1983 | 4.887 | 4.8416 | 12 | 6.371 | 6.3118 | 12 | 0.9% | -0.25 [-1.06, 0.55] |
| Grizenko 2012 | 54.38 | 11.13 | 198 | 63.76 | 14.38 | 198 | 1.9% | -0.73 [-0.93, -0.52] |
| Hoeppner 1997 | 8.2 | 6.85 | 50 | 14.23 | 8.31 | 50 | 1.6% | -0.79 [-1.19, -0.38] |
| Ialongo 1994 | 7.53 | 7.41 | 13 | 15.25 | 7.27 | 12 | 0.9% | -1.02 [-1.86, -0.17] |
| Jensen 1999 (MTA) | 0.75 | 0.71 | 134 | 1.1 | 0.77 | 119 | 1.9% | -0.47 [-0.72, -0.22] |
| Kaplan 1990 | 0.9 | 0.8 | 6 | 1.7 | 0.9 | 6 | 0.6% | -0.87 [-2.08, 0.34] |
| Kolko 1999 | 3.3 | 2.9 | 22 | 9.9 | 3.8 | 22 | 1.1% | -1.92 [-2.64, -1.19] |
| Kollins 2006 (PATS) | 1.09 | 0.8 | 32 | 1.35 | 0.77 | 32 | 1.4% | -0.33 [-0.82, 0.17] |
| Konrad 2004 | 26.3 | 5.2 | 60 | 42.5 | 6.1 | 60 | 1.4% | -2.84 [-3.35, -2.33] |



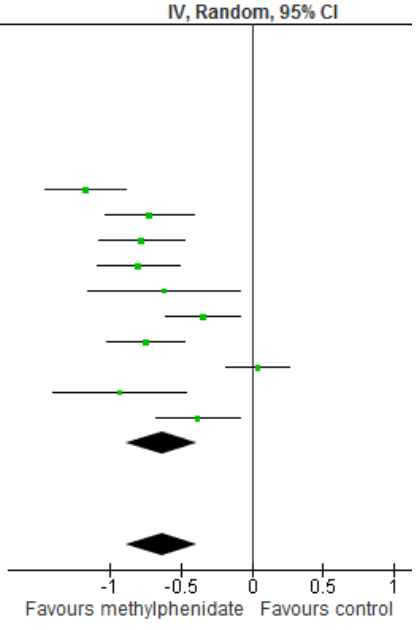
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Konrad 2005 | 14.3 | 10.1 | 44 | 22.2 | 13.8 | 44 | 1.6% | -0.65 [-1.08, -0.22] |
| Lehmkuhl 2002 | 0.9 | 0.6557 | 43 | 1.6 | 0.6481 | 42 | 1.5% | -1.06 [-1.52, -0.61] |
| Lufi 1997 | 30.85 | 15.19 | 20 | 32.6 | 12.75 | 20 | 1.2% | -0.12 [-0.74, 0.50] |
| Lufi 2007 | 6.97 | 3.8 | 19 | 12.56 | 6.69 | 19 | 1.1% | -1.01 [-1.69, -0.33] |
| Manos 1999 | 56.12 | 11.81 | 117 | 64.38 | 15.41 | 117 | 1.9% | -0.60 [-0.86, -0.34] |
| McBride 1988a | 7.5 | 4.5 | 46 | 17 | 6.5 | 46 | 1.5% | -1.69 [-2.16, -1.21] |
| McGough 2006 | 3.2 | 5.1877 | 80 | 8 | 5.1877 | 80 | 1.7% | -0.92 [-1.25, -0.59] |
| Moshe 2012 | 58 | 10.3 | 57 | 64.7 | 12.5 | 57 | 1.7% | -0.58 [-0.96, -0.21] |
| Palumbo 2008 | -5.07 | 6.79 | 29 | -3.2 | 6.38 | 30 | 1.4% | -0.28 [-0.79, 0.23] |
| Pearson 2013 | 59.3 | 12.7 | 24 | 75.6 | 11.5 | 24 | 1.2% | -1.32 [-1.95, -0.69] |
| Pelham 1989 | 2.45 | 3.8669 | 24 | 4.2 | 6.624 | 24 | 1.3% | -0.32 [-0.89, 0.25] |
| Pelham 1990a | 2.3 | 2 | 22 | 3.8 | 4.6 | 22 | 1.3% | -0.42 [-1.01, 0.18] |
| Pelham 1993a | 2 | 2.1 | 31 | 6 | 4.3 | 31 | 1.3% | -1.17 [-1.71, -0.63] |
| Pelham 1999 | 1.1 | 1.2 | 25 | 3.7 | 2.6 | 25 | 1.2% | -1.26 [-1.88, -0.65] |
| Pelham 2001a | 7.94 | 5.83 | 68 | 16.4 | 7.74 | 68 | 1.7% | -1.23 [-1.60, -0.86] |
| Pelham 2002 | 1.8 | 1.7 | 136 | 3.5 | 2.9 | 136 | 1.9% | -0.71 [-0.96, -0.47] |
| Pelham 2005 | 2.3 | 2.7 | 29 | 5.7 | 5.9 | 29 | 1.4% | -0.73 [-1.26, -0.20] |
| Pelham 2011 | 6 | 4.3 | 10 | 9.7 | 51 | 10 | 0.9% | -0.10 [-0.98, 0.78] |
| Pliszka 1990 | 13.8 | 8.8 | 30 | 25.2 | 15.3 | 30 | 1.4% | -0.90 [-1.43, -0.37] |
| Pliszka 2000 | 0.81 | 0.62 | 20 | 1.49 | 0.87 | 18 | 1.1% | -0.89 [-1.56, -0.22] |
| Quinn 2004 | 1.58 | 3.85 | 32 | 6.39 | 6.81 | 32 | 1.4% | -0.86 [-1.37, -0.35] |
| Rapport 1987 | 7.16 | 5 | 31 | 15.84 | 5.06 | 31 | 1.3% | -1.70 [-2.29, -1.12] |
| Schachar 1997a | 0.9 | 0.7 | 37 | 1.7 | 0.7 | 29 | 1.4% | -1.13 [-1.65, -0.60] |
| Silva 2008 | 1.4 | 2.46 | 68 | 5.86 | 4.68 | 68 | 1.7% | -1.19 [-1.55, -0.82] |
| Smith 1998 | 1.2 | 1.5 | 45 | 4.4 | 3.5 | 45 | 1.5% | -1.18 [-1.63, -0.73] |
| Smith 2004 | 10.3 | 0.2108 | 1 | 15.3 | 0.1031 | 1 | | Not estimable |
| Smithee 1998 | 0.647 | 0.51 | 25 | 1.1249 | 0.5766 | 25 | 1.3% | -0.86 [-1.45, -0.28] |
| Solanto 2009 | 60.06 | 10.57 | 30 | 63.28 | 10.55 | 30 | 1.4% | -0.30 [-0.81, 0.21] |
| Taylor 1987 | 0.54 | 1.04 | 39 | 1.22 | 1.3 | 39 | 1.5% | -0.57 [-1.03, -0.12] |
| Tirosh 1993a | 17.6 | 6.3 | 20 | 32 | 9.2 | 20 | 1.0% | -1.79 [-2.53, -1.05] |
| Ullmann 1986 | -45.6 | 19.2 | 118 | -11.3 | 15.1 | 118 | 1.8% | -1.98 [-2.29, -1.67] |
| Van der Meere 1999a | 73.6 | 12.7133 | 24 | 83.1 | 12.7133 | 24 | 1.3% | -0.73 [-1.32, -0.15] |
| Wigal 2013 | 7.1 | 5.64 | 44 | 19.3 | 8.38 | 44 | 1.4% | -1.69 [-2.18, -1.20] |
| Wilens 2008 | 15.4 | 10.7354 | 120 | 24.5 | 10.7354 | 120 | 1.9% | -0.84 [-1.11, -0.58] |
| Wolraich 2001 | 5.7 | 3.84 | 81 | 9.87 | 4.09 | 46 | 1.6% | -1.05 [-1.44, -0.67] |
| Zeiner 1999 | 8.83 | 6.49 | 38 | 14.69 | 6.17 | 38 | 1.5% | -0.92 [-1.39, -0.44] |
| **Subtotal (95% CI)** | | | **3137** | | | **3003** | **95.0%** | **-0.92 [-1.03, -0.81]** |
| Heterogeneity: Tau² = 0.14; Chi² = 252.17, df = 69 (P < 0.00001); I² = 73% | | | | | | | | |
| Test for overall effect: Z = 16.60 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **3239** | | | **3105** | **100.0%** | **-0.91 [-1.01, -0.80]** |
| Heterogeneity: Tau² = 0.14; Chi² = 259.30, df = 73 (P < 0.00001); I² = 72% | | | | | | | | |
| Test for overall effect: Z = 16.88 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 2.43, df = 1 (P = 0.12), I² = 58.9% | | | | | | | | |



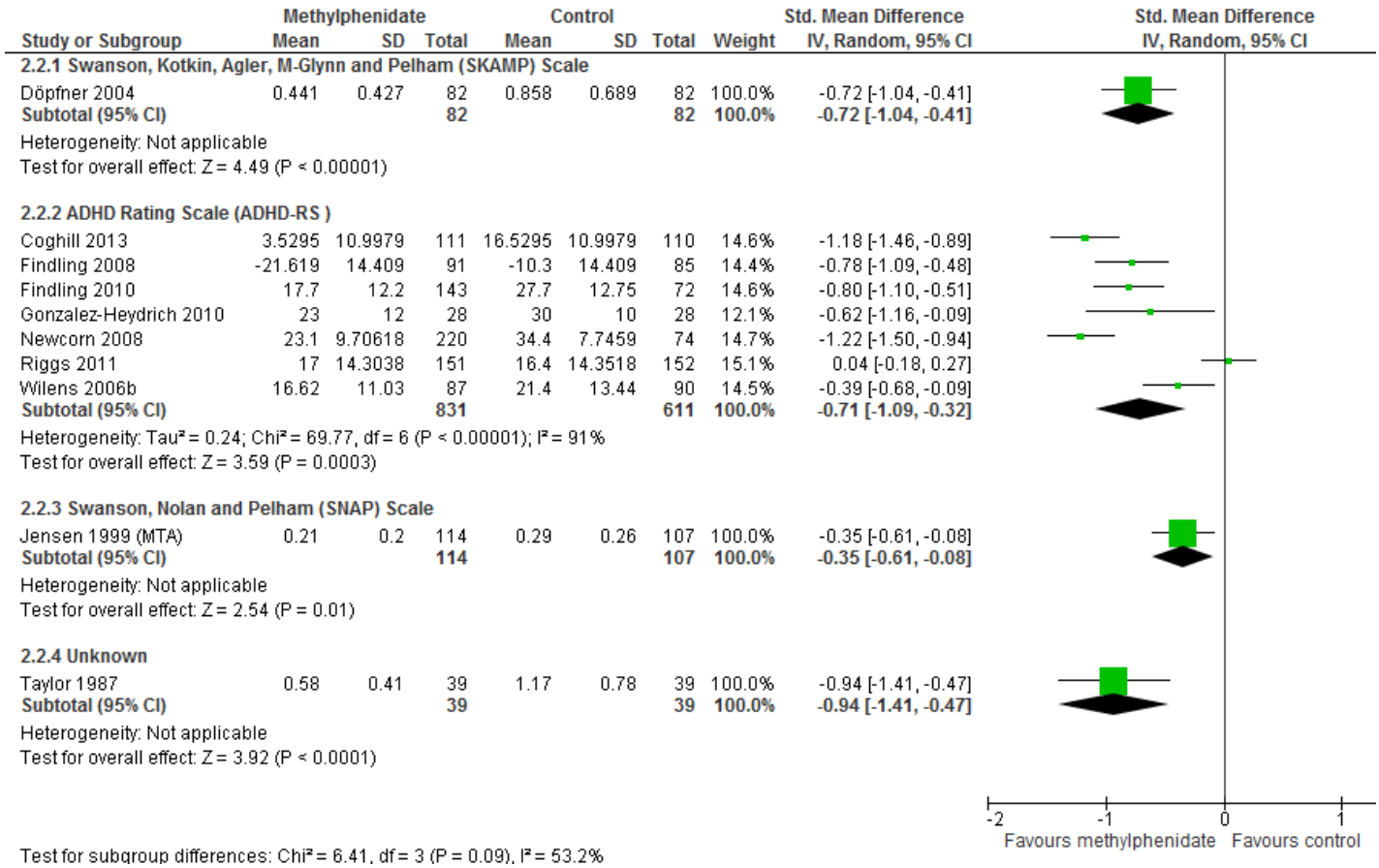

## 2 - Independent assessor-rated ADHD symptoms

**2.1 All parallel-group trials and first-period cross-over trials**

| | Methylphenidate | | | Control | | | | Std. Mean Difference |
|---|---|---|---|---|---|---|---|---|
| **Study or Subgroup** | **Mean** | **SD** | **Total** | **Mean** | **SD** | **Total** | **Weight** | **IV, Random, 95% CI** |
| **2.1.1 Low risk of bias** | | | | | | | | |
| **Subtotal (95% CI)** | | | **0** | | | **0** | | **Not estimable** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | | |
| **2.1.2 High risk of bias** | | | | | | | | |
| Coghill 2013 | 3.5295 | 10.9979 | 111 | 16.5295 | 10.9979 | 110 | 10.4% | -1.18 [-1.46, -0.89] |
| Döpfner 2004 | 0.441 | 0.427 | 82 | 0.858 | 0.689 | 82 | 10.1% | -0.72 [-1.04, -0.41] |
| Findling 2008 | -21.619 | 14.409 | 91 | -10.3 | 14.409 | 85 | 10.2% | -0.78 [-1.09, -0.48] |
| Findling 2010 | 17.7 | 12.2 | 145 | 27.7 | 12.75 | 72 | 10.4% | -0.80 [-1.10, -0.51] |
| Gonzalez-Heydrich 2010 | 23 | 12 | 28 | 30 | 10 | 28 | 7.7% | -0.62 [-1.16, -0.09] |
| Jensen 1999 (MTA) | 0.21 | 0.2 | 114 | 0.29 | 0.26 | 107 | 10.6% | -0.35 [-0.61, -0.08] |
| Newcorn 2008 | -16.9 | 13.1 | 220 | -7.3 | 11.5 | 74 | 10.6% | -0.75 [-1.02, -0.48] |
| Riggs 2011 | 17 | 14.3038 | 151 | 16.4 | 14.3518 | 152 | 11.0% | 0.04 [-0.18, 0.27] |
| Taylor 1987 | 0.58 | 0.41 | 39 | 1.17 | 0.78 | 39 | 8.5% | -0.94 [-1.41, -0.47] |
| Wilens 2006b | 16.62 | 11.03 | 87 | 21.4 | 13.44 | 90 | 10.3% | -0.39 [-0.68, -0.09] |
| **Subtotal (95% CI)** | | | **1068** | | | **839** | **100.0%** | **-0.64 [-0.89, -0.39]** |
| Heterogeneity: Tau² = 0.13; Chi² = 59.25, df = 9 (P < 0.00001); I² = 85% | | | | | | | | |
| Test for overall effect: Z = 5.04 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **1068** | | | **839** | **100.0%** | **-0.64 [-0.89, -0.39]** |
| Heterogeneity: Tau² = 0.13; Chi² = 59.25, df = 9 (P < 0.00001); I² = 85% | | | | | | | | |
| Test for overall effect: Z = 5.04 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | |

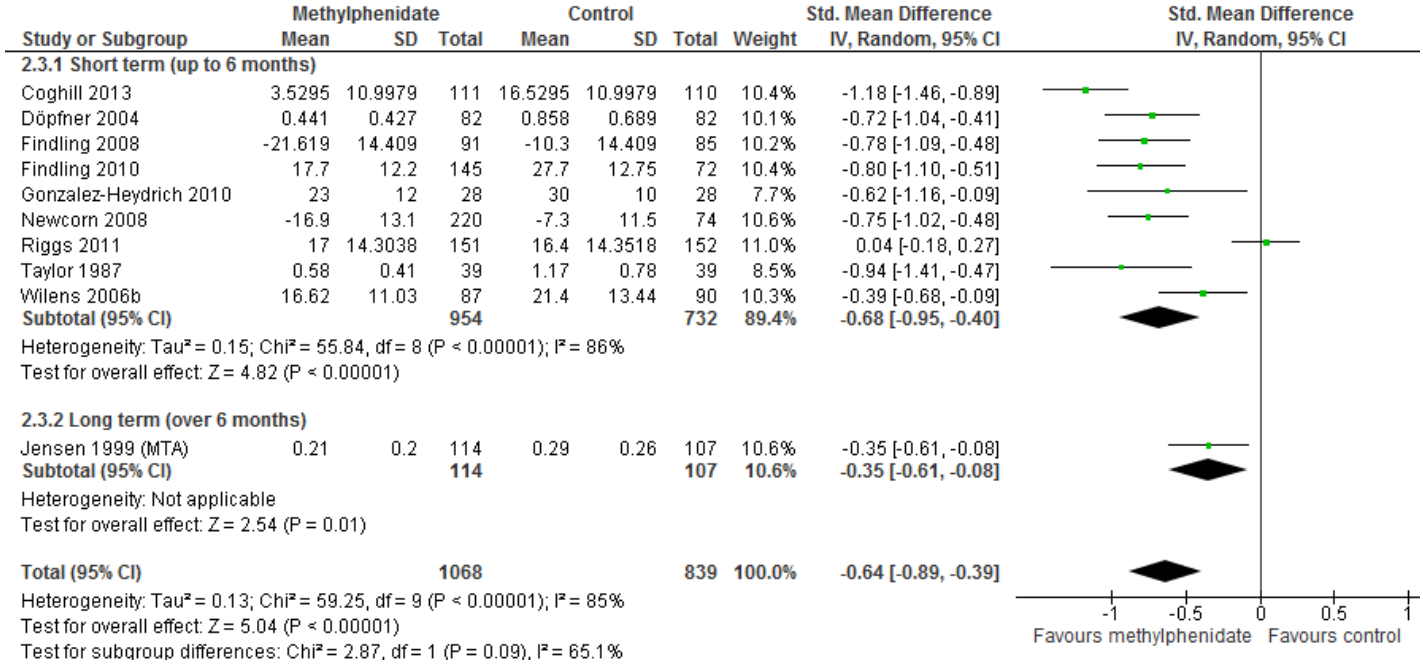


### 2.2 Subgroup analysis: types of scales



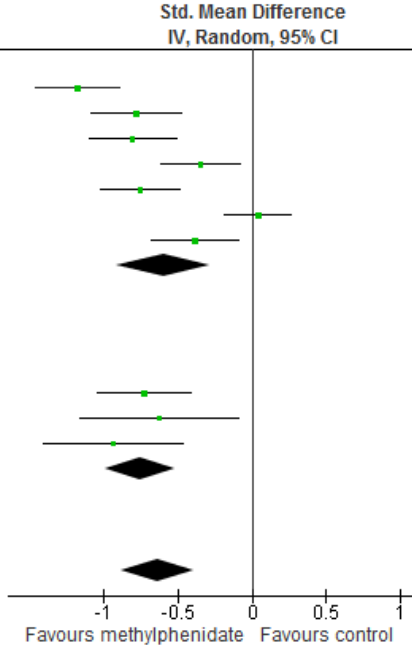

Test for subgroup differences: Chi² = 6.41, df = 3 (P = 0.09), I² = 53.2%

### 2.3 Subgroup analysis: duration of treatment



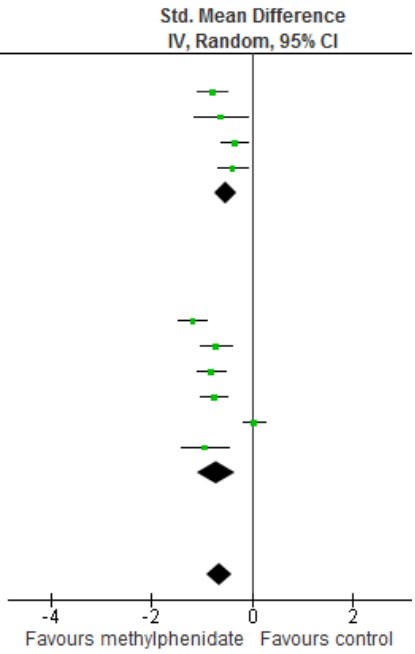
**2.4 Subgroup analysis: parallel-group trials compared with first-period cross-over trials**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **2.4.1 Parallel-group trials** | | | | | | | | |
| Coghill 2013 | 3.5295 | 10.9979 | 111 | 16.5295 | 10.9979 | 110 | 10.4% | -1.18 [-1.46, -0.89] |
| Findling 2008 | -21.619 | 14.409 | 91 | -10.3 | 14.409 | 85 | 10.2% | -0.78 [-1.09, -0.48] |
| Findling 2010 | 17.7 | 12.2 | 145 | 27.7 | 12.75 | 72 | 10.4% | -0.80 [-1.10, -0.51] |
| Jensen 1999 (MTA) | 0.21 | 0.2 | 114 | 0.29 | 0.26 | 107 | 10.6% | -0.35 [-0.61, -0.08] |
| Newcorn 2008 | -16.9 | 13.1 | 220 | -7.3 | 11.5 | 74 | 10.6% | -0.75 [-1.02, -0.48] |
| Riggs 2011 | 17 | 14.3038 | 151 | 16.4 | 14.3518 | 152 | 11.0% | 0.04 [-0.18, 0.27] |
| Wilens 2006b | 16.62 | 11.03 | 87 | 21.4 | 13.44 | 90 | 10.3% | -0.39 [-0.68, -0.09] |
| **Subtotal (95% CI)** | | | **919** | | | **690** | **73.7%** | **-0.60 [-0.91, -0.28]** |
| Heterogeneity: Tau² = 0.16; Chi² = 55.74, df = 6 (P < 0.00001); I² = 89% | | | | | | | | |
| Test for overall effect: Z = 3.69 (P = 0.0002) | | | | | | | | |
| **2.4.2 First-period cross-over trials** | | | | | | | | |
| Döpfner 2004 | 0.441 | 0.427 | 82 | 0.858 | 0.689 | 82 | 10.1% | -0.72 [-1.04, -0.41] |
| Gonzalez-Heydrich 2010 | 23 | 12 | 28 | 30 | 10 | 28 | 7.7% | -0.62 [-1.16, -0.09] |
| Taylor 1987 | 0.58 | 0.41 | 39 | 1.17 | 0.78 | 39 | 8.5% | -0.94 [-1.41, -0.47] |
| **Subtotal (95% CI)** | | | **149** | | | **149** | **26.3%** | **-0.76 [-0.99, -0.52]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.84, df = 2 (P = 0.66); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 6.31 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **1068** | | | **839** | **100.0%** | **-0.64 [-0.89, -0.39]** |
| Heterogeneity: Tau² = 0.13; Chi² = 59.25, df = 9 (P < 0.00001); I² = 85% | | | | | | | | |
| Test for overall effect: Z = 5.04 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.65, df = 1 (P = 0.42), I² = 0% | | | | | | | | |



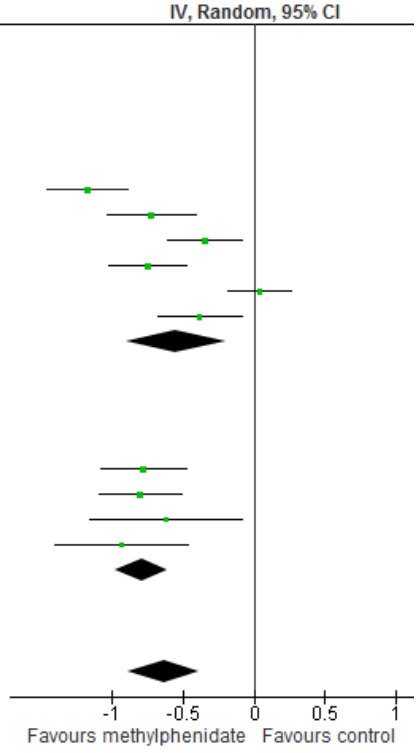

**2.5 Subgroup analysis: trials with cohort selection bias of all participants compared with trials without cohort selection bias of all participants**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **2.5.1 Trials with cohort selection bias of all participants** | | | | | | | | |
| Findling 2008 | -21.619 | 14.409 | 91 | -10.3 | 14.409 | 85 | 10.2% | -0.78 [-1.09, -0.48] |
| Gonzalez-Heydrich 2010 | 23 | 12 | 28 | 30 | 10 | 28 | 7.7% | -0.62 [-1.16, -0.09] |
| Jensen 1999 (MTA) | 0.21 | 0.2 | 114 | 0.29 | 0.26 | 107 | 10.6% | -0.35 [-0.61, -0.08] |
| Wilens 2006b | 16.62 | 11.03 | 87 | 21.4 | 13.44 | 90 | 10.3% | -0.39 [-0.68, -0.09] |
| **Subtotal (95% CI)** | | | **320** | | | **310** | **38.9%** | **-0.51 [-0.73, -0.29]** |
| Heterogeneity: Tau² = 0.02; Chi² = 5.32, df = 3 (P = 0.15); I² = 44% | | | | | | | | |
| Test for overall effect: Z = 4.57 (P < 0.00001) | | | | | | | | |
| **2.5.2 Trials without cohort selection bias of all participants** | | | | | | | | |
| Coghill 2013 | 3.5295 | 10.9979 | 111 | 16.5295 | 10.9979 | 110 | 10.4% | -1.18 [-1.46, -0.89] |
| Döpfner 2004 | 0.441 | 0.427 | 82 | 0.858 | 0.689 | 82 | 10.1% | -0.72 [-1.04, -0.41] |
| Findling 2010 | 17.7 | 12.2 | 145 | 27.7 | 12.75 | 72 | 10.4% | -0.80 [-1.10, -0.51] |
| Newcorn 2008 | -16.9 | 13.1 | 220 | -7.3 | 11.5 | 74 | 10.6% | -0.75 [-1.02, -0.48] |
| Riggs 2011 | 17 | 14.3038 | 151 | 16.4 | 14.3518 | 152 | 11.0% | 0.04 [-0.18, 0.27] |
| Taylor 1987 | 0.58 | 0.41 | 39 | 1.17 | 0.78 | 39 | 8.5% | -0.94 [-1.41, -0.47] |
| **Subtotal (95% CI)** | | | **748** | | | **529** | **61.1%** | **-0.72 [-1.11, -0.33]** |
| Heterogeneity: Tau² = 0.21; Chi² = 52.42, df = 5 (P < 0.00001); I² = 90% | | | | | | | | |
| Test for overall effect: Z = 3.60 (P = 0.0003) | | | | | | | | |
| **Total (95% CI)** | | | **1068** | | | **839** | **100.0%** | **-0.64 [-0.89, -0.39]** |
| Heterogeneity: Tau² = 0.13; Chi² = 59.25, df = 9 (P < 0.00001); I² = 85% | | | | | | | | |
| Test for overall effect: Z = 5.04 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.80, df = 1 (P = 0.37), I² = 0% | | | | | | | | |



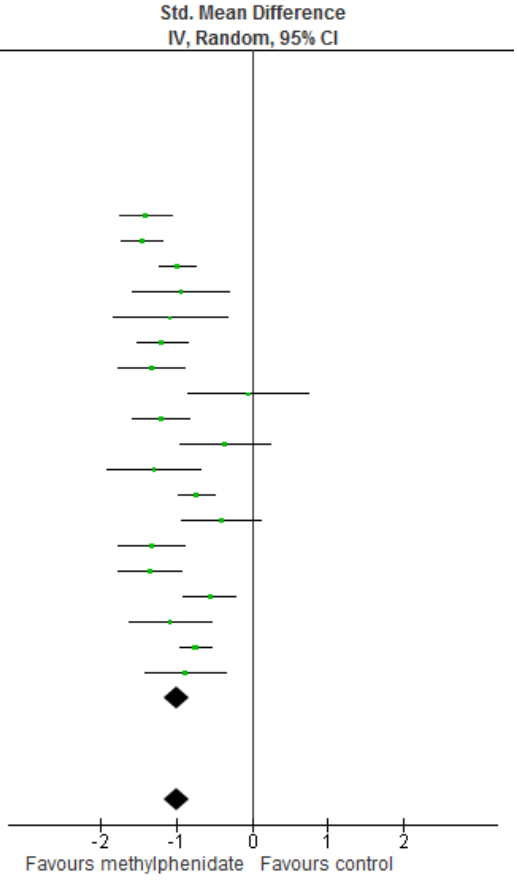
**2.6 Subgroup analysis: dose**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **2.6.1 Low dose** | | | | | | | | |
| **Subtotal (95% CI)** | | | **0** | | | **0** | | **Not estimable** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | | |
| **2.6.2 High dose** | | | | | | | | |
| Coghill 2013 | 3.5295 | 10.9979 | 111 | 16.5295 | 10.9979 | 110 | 10.4% | -1.18 [-1.46, -0.89] |
| Döpfner 2004 | 0.441 | 0.427 | 82 | 0.858 | 0.689 | 82 | 10.1% | -0.72 [-1.04, -0.41] |
| Jensen 1999 (MTA) | 0.21 | 0.2 | 114 | 0.29 | 0.26 | 107 | 10.6% | -0.35 [-0.61, -0.08] |
| Newcorn 2008 | -16.9 | 13.1 | 220 | -7.3 | 11.5 | 74 | 10.6% | -0.75 [-1.02, -0.48] |
| Riggs 2011 | 17 | 14.3038 | 151 | 16.4 | 14.3518 | 152 | 11.0% | 0.04 [-0.18, 0.27] |
| Wilens 2006b | 16.62 | 11.03 | 87 | 21.4 | 13.44 | 90 | 10.3% | -0.39 [-0.68, -0.09] |
| **Subtotal (95% CI)** | | | **765** | | | **615** | **63.2%** | **-0.55 [-0.91, -0.20]** |
| Heterogeneity: Tau² = 0.18; Chi² = 50.96, df = 5 (P < 0.00001); I² = 90% | | | | | | | | |
| Test for overall effect: Z = 3.03 (P = 0.002) | | | | | | | | |
| **2.6.3 Unknown dose** | | | | | | | | |
| Findling 2008 | -21.619 | 14.409 | 91 | -10.3 | 14.409 | 85 | 10.2% | -0.78 [-1.09, -0.48] |
| Findling 2010 | 17.7 | 12.2 | 145 | 27.7 | 12.75 | 72 | 10.4% | -0.80 [-1.10, -0.51] |
| Gonzalez-Heydrich 2010 | 23 | 12 | 28 | 30 | 10 | 28 | 7.7% | -0.62 [-1.16, -0.09] |
| Taylor 1987 | 0.58 | 0.41 | 39 | 1.17 | 0.78 | 39 | 8.5% | -0.94 [-1.41, -0.47] |
| **Subtotal (95% CI)** | | | **303** | | | **224** | **36.8%** | **-0.80 [-0.98, -0.61]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 3 (P = 0.86); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 8.59 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **1068** | | | **839** | **100.0%** | **-0.64 [-0.89, -0.39]** |
| Heterogeneity: Tau² = 0.13; Chi² = 59.25, df = 9 (P < 0.00001); I² = 85% | | | | | | | | |
| Test for overall effect: Z = 5.04 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 1.42, df = 1 (P = 0.23), I² = 29.5% | | | | | | | | |



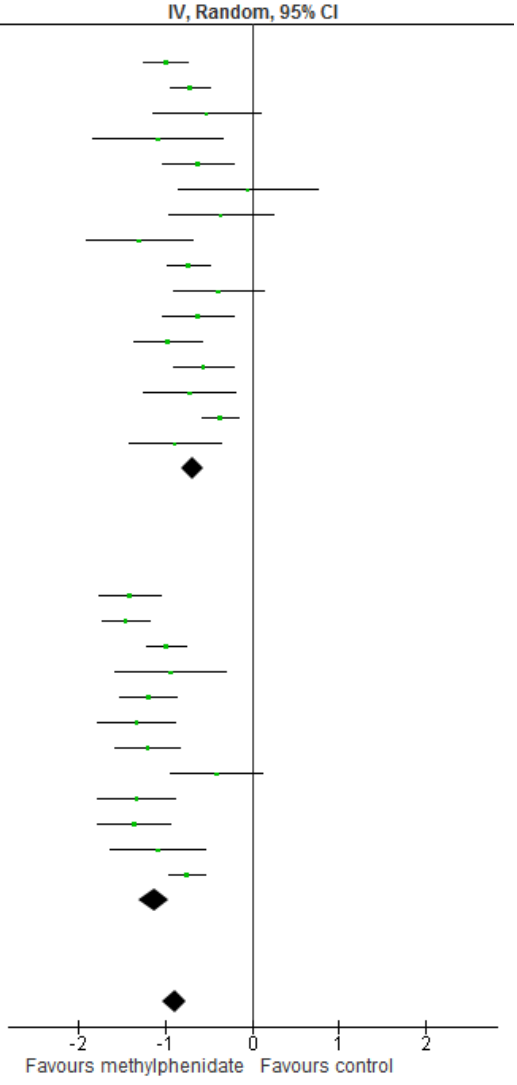

**2.7 ADHD symptoms, cross-over trials (endpoint data), subgroup analysis: risk of bias**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **2.7.1 Low risk of bias** | | | | | | | | |
| **Subtotal (95% CI)** | | | **0** | | | **0** | | **Not estimable** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | | |
| **2.7.2 High risk of bias** | | | | | | | | |
| Armstrong 2012 | 9.8 | 7.7719 | 78 | 20.8 | 7.7719 | 78 | 6.1% | -1.41 [-1.76, -1.06] |
| Bedard 2008 | 2.22 | 2.17 | 130 | 6.51 | 3.54 | 130 | 6.9% | -1.46 [-1.73, -1.18] |
| Brams 2012 | -4.47 | 9.1005 | 158 | 4.5 | 9.088 | 158 | 7.3% | -0.98 [-1.22, -0.75] |
| Chronis 2003 | 3.3 | 1.7 | 21 | 5.8 | 3.3 | 21 | 3.7% | -0.93 [-1.57, -0.29] |
| Douglas 1986 | 0.47 | 0.42 | 16 | 1.07 | 0.64 | 16 | 3.0% | -1.08 [-1.83, -0.33] |
| Döpfner 2004 | 0.374 | 0.366 | 82 | 1.081 | 0.751 | 82 | 6.3% | -1.19 [-1.52, -0.86] |
| Fabiano 2007 | 2.3 | 1.5 | 48 | 6 | 3.6 | 48 | 5.2% | -1.33 [-1.77, -0.89] |
| Kent 1995 | 2.7 | 2.3 | 12 | 2.8 | 1.9 | 12 | 2.8% | -0.05 [-0.85, 0.75] |
| Murray 2011 | 8.7 | 7.7761 | 67 | 18.1 | 7.76 | 64 | 5.9% | -1.20 [-1.58, -0.83] |
| Pelham 1990a | 4.81 | 3.2 | 22 | 6.3 | 4.8 | 22 | 4.0% | -0.36 [-0.95, 0.24] |
| Pelham 1999 | 2.6 | 1.4 | 25 | 5.6 | 2.9 | 25 | 3.9% | -1.30 [-1.91, -0.68] |
| Pelham 2002 | 3 | 1.4 | 136 | 4.4 | 2.3 | 136 | 7.2% | -0.73 [-0.98, -0.49] |
| Pelham 2005 | 5.1 | 3.8 | 29 | 6.9 | 4.8 | 29 | 4.6% | -0.41 [-0.93, 0.11] |
| Pelham 2014 | 2.3 | 1.5 | 47 | 6 | 3.6 | 47 | 5.2% | -1.33 [-1.78, -0.88] |
| Silva 2005a | 0.67 | 0.58 | 54 | 1.94 | 1.18 | 54 | 5.5% | -1.36 [-1.78, -0.94] |
| Silva 2008 | 2.24 | 9.8542 | 68 | 7.77 | 9.7965 | 68 | 6.2% | -0.56 [-0.90, -0.22] |
| Solanto 2009 | 15.21 | 9.21 | 30 | 26.58 | 11.39 | 30 | 4.4% | -1.08 [-1.63, -0.54] |
| Swanson 2004b | 12.62 | 11 | 184 | 22.11 | 14.1 | 184 | 7.5% | -0.75 [-0.96, -0.54] |
| Wilens 2010 | 14.76 | 14.48 | 30 | 28.33 | 15.75 | 30 | 4.5% | -0.89 [-1.42, -0.35] |
| **Subtotal (95% CI)** | | | **1237** | | | **1234** | **100.0%** | **-1.00 [-1.16, -0.84]** |
| Heterogeneity: Tau² = 0.08; Chi² = 57.64, df = 18 (P < 0.00001); I² = 69% | | | | | | | | |
| Test for overall effect: Z = 12.05 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **1237** | | | **1234** | **100.0%** | **-1.00 [-1.16, -0.84]** |
| Heterogeneity: Tau² = 0.08; Chi² = 57.64, df = 18 (P < 0.00001); I² = 69% | | | | | | | | |
| Test for overall effect: Z = 12.05 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | |



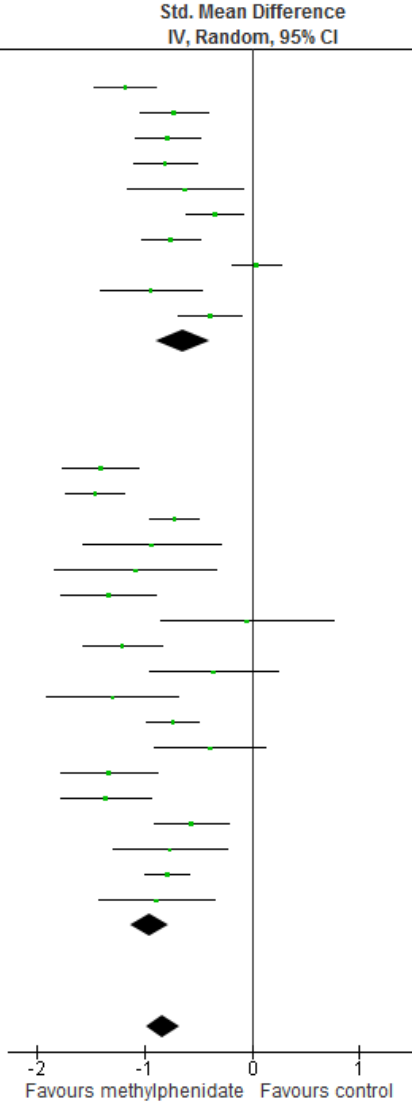
**2.8 ADHD symptoms, cross-over trials (endpoint data), subgroup analysis: dose**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **2.8.1 Low dose** | | | | | | | | |
| Bedard 2008 | 3.39 | 2.65 | 130 | 6.51 | 3.54 | 130 | 4.6% | -0.99 [-1.25, -0.74] |
| Brams 2012 | -2.02 | 9.041 | 159 | 4.5 | 9.088 | 158 | 4.8% | -0.72 [-0.94, -0.49] |
| Chronis 2003 | 4.3 | 2.2 | 21 | 5.8 | 3.3 | 21 | 2.6% | -0.52 [-1.14, 0.09] |
| Douglas 1986 | 0.47 | 0.42 | 16 | 1.07 | 0.64 | 16 | 2.1% | -1.08 [-1.83, -0.33] |
| Fabiano 2007 | 4 | 2.7 | 48 | 6 | 3.6 | 48 | 3.7% | -0.62 [-1.03, -0.21] |
| Kent 1995 | 2.7 | 2.3 | 12 | 2.8 | 1.9 | 12 | 1.9% | -0.05 [-0.85, 0.75] |
| Pelham 1990a | 4.81 | 3.2 | 22 | 6.3 | 4.8 | 22 | 2.7% | -0.36 [-0.95, 0.24] |
| Pelham 1999 | 2.6 | 1.4 | 25 | 5.6 | 2.9 | 25 | 2.6% | -1.30 [-1.91, -0.68] |
| Pelham 2002 | 3 | 1.4 | 136 | 4.4 | 2.3 | 136 | 4.7% | -0.73 [-0.98, -0.49] |
| Pelham 2005 | 5.2 | 3.8 | 29 | 6.9 | 4.8 | 29 | 3.0% | -0.39 [-0.91, 0.13] |
| Pelham 2014 | 4 | 2.7 | 47 | 6 | 3.6 | 47 | 3.6% | -0.62 [-1.04, -0.21] |
| Silva 2005a | 0.99 | 0.71 | 54 | 1.94 | 1.18 | 54 | 3.7% | -0.97 [-1.37, -0.57] |
| Silva 2008 | 2.24 | 9.8542 | 68 | 7.77 | 9.7965 | 68 | 4.1% | -0.56 [-0.90, -0.22] |
| Solanto 2009 | 18.63 | 10.45 | 30 | 26.58 | 11.39 | 30 | 3.0% | -0.72 [-1.24, -0.19] |
| Swanson 2004b | 16.44 | 12.43 | 184 | 21.47 | 14.61 | 184 | 4.9% | -0.37 [-0.58, -0.16] |
| Wilens 2010 | 14.76 | 14.48 | 30 | 28.33 | 15.75 | 30 | 3.0% | -0.89 [-1.42, -0.35] |
| **Subtotal (95% CI)** | | | **1011** | | | **1010** | **54.9%** | **-0.69 [-0.82, -0.55]** |
| Heterogeneity: Tau² = 0.03; Chi² = 27.84, df = 15 (P = 0.02); I² = 46% | | | | | | | | |
| Test for overall effect: Z = 9.94 (P < 0.00001) | | | | | | | | |
| **2.8.2 High dose** | | | | | | | | |
| Armstrong 2012 | 9.8 | 7.7719 | 78 | 20.8 | 7.7719 | 78 | 4.0% | -1.41 [-1.76, -1.06] |
| Bedard 2008 | 2.22 | 2.17 | 130 | 6.51 | 3.54 | 130 | 4.5% | -1.46 [-1.73, -1.18] |
| Brams 2012 | -4.47 | 9.1005 | 158 | 4.5 | 9.088 | 158 | 4.7% | -0.98 [-1.22, -0.75] |
| Chronis 2003 | 3.3 | 1.7 | 21 | 5.8 | 3.3 | 21 | 2.5% | -0.93 [-1.57, -0.29] |
| Döpfner 2004 | 0.374 | 0.366 | 82 | 1.081 | 0.751 | 82 | 4.1% | -1.19 [-1.52, -0.86] |
| Fabiano 2007 | 2.3 | 1.5 | 48 | 6 | 3.6 | 48 | 3.5% | -1.33 [-1.77, -0.89] |
| Murray 2011 | 8.7 | 7.7761 | 67 | 18.1 | 7.76 | 64 | 3.9% | -1.20 [-1.58, -0.83] |
| Pelham 2005 | 5.1 | 3.8 | 29 | 6.9 | 4.8 | 29 | 3.0% | -0.41 [-0.93, 0.11] |
| Pelham 2014 | 2.3 | 1.5 | 47 | 6 | 3.6 | 47 | 3.4% | -1.33 [-1.78, -0.88] |
| Silva 2005a | 0.67 | 0.58 | 54 | 1.94 | 1.18 | 54 | 3.6% | -1.36 [-1.78, -0.94] |
| Solanto 2009 | 15.21 | 9.21 | 30 | 26.58 | 11.39 | 30 | 2.9% | -1.08 [-1.63, -0.54] |
| Swanson 2004b | 12.62 | 11 | 184 | 22.11 | 14.1 | 184 | 4.9% | -0.75 [-0.96, -0.54] |
| **Subtotal (95% CI)** | | | **928** | | | **925** | **45.1%** | **-1.13 [-1.31, -0.95]** |
| Heterogeneity: Tau² = 0.06; Chi² = 32.09, df = 11 (P = 0.0007); I² = 66% | | | | | | | | |
| Test for overall effect: Z = 12.39 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **1939** | | | **1935** | **100.0%** | **-0.89 [-1.02, -0.75]** |
| Heterogeneity: Tau² = 0.09; Chi² = 98.88, df = 27 (P < 0.00001); I² = 73% | | | | | | | | |
| Test for overall effect: Z = 12.77 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 15.11, df = 1 (P = 0.0001), I² = 93.4% | | | | | | | | |



**2.9 Subgroup analysis: all parallel-group trials and first-period cross-over trials compared with cross-over trials (endpoint data)**

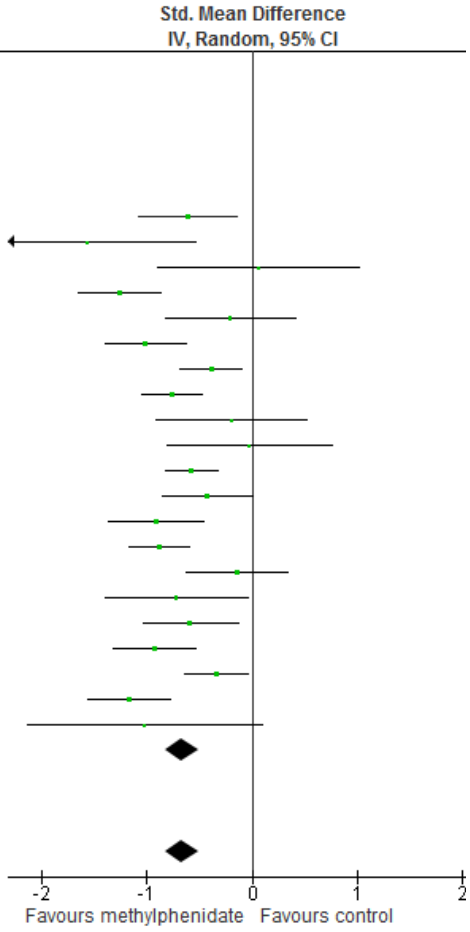
| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **2.9.1 All parallel-group trials and first-period cross-over trials** | | | | | | | | |
| Coghill 2013 | 3.5295 | 10.9979 | 111 | 16.5295 | 10.9979 | 110 | 4.1% | -1.18 [-1.46, -0.89] |
| Döpfner 2004 | 0.441 | 0.427 | 82 | 0.858 | 0.689 | 82 | 4.0% | -0.72 [-1.04, -0.41] |
| Findling 2008 | -21.619 | 14.409 | 91 | -10.3 | 14.409 | 85 | 4.0% | -0.78 [-1.09, -0.48] |
| Findling 2010 | 17.7 | 12.2 | 145 | 27.7 | 12.75 | 72 | 4.1% | -0.80 [-1.10, -0.51] |
| Gonzalez-Heydrich 2010 | 23 | 12 | 28 | 30 | 10 | 28 | 3.1% | -0.62 [-1.16, -0.09] |
| Jensen 1999 (MTA) | 0.21 | 0.2 | 114 | 0.29 | 0.26 | 107 | 4.2% | -0.35 [-0.61, -0.08] |
| Newcorn 2008 | -16.9 | 13.1 | 220 | -7.3 | 11.5 | 74 | 4.1% | -0.75 [-1.02, -0.48] |
| Riggs 2011 | 17 | 14.3038 | 151 | 16.4 | 14.3518 | 152 | 4.3% | 0.04 [-0.18, 0.27] |
| Taylor 1987 | 0.58 | 0.41 | 39 | 1.17 | 0.78 | 39 | 3.3% | -0.94 [-1.41, -0.47] |
| Wilens 2006b | 16.62 | 11.03 | 87 | 21.4 | 13.44 | 90 | 4.0% | -0.39 [-0.68, -0.09] |
| **Subtotal (95% CI)** | | | **1068** | | | **839** | **39.2%** | **-0.64 [-0.89, -0.39]** |
| Heterogeneity: Tau² = 0.13; Chi² = 59.25, df = 9 (P < 0.00001); I² = 85% | | | | | | | | |
| Test for overall effect: Z = 5.04 (P < 0.00001) | | | | | | | | |
| **2.9.2 Cross-over trials (endpoint data)** | | | | | | | | |
| Armstrong 2012 | 9.8 | 7.7719 | 78 | 20.8 | 7.7719 | 78 | 3.8% | -1.41 [-1.76, -1.06] |
| Bedard 2008 | 2.22 | 2.17 | 130 | 6.51 | 3.54 | 130 | 4.1% | -1.46 [-1.73, -1.18] |
| Brams 2012 | -2.02 | 9.041 | 159 | 4.5 | 9.088 | 158 | 4.3% | -0.72 [-0.94, -0.49] |
| Chronis 2003 | 3.3 | 1.7 | 21 | 5.8 | 3.3 | 21 | 2.7% | -0.93 [-1.57, -0.29] |
| Douglas 1986 | 0.47 | 0.42 | 16 | 1.07 | 0.64 | 16 | 2.3% | -1.08 [-1.83, -0.33] |
| Fabiano 2007 | 2.3 | 1.5 | 48 | 6 | 3.6 | 48 | 3.4% | -1.33 [-1.77, -0.89] |
| Kent 1995 | 2.7 | 2.3 | 12 | 2.8 | 1.9 | 12 | 2.1% | -0.05 [-0.85, 0.75] |
| Murray 2011 | 8.7 | 7.7761 | 67 | 18.1 | 7.76 | 64 | 3.7% | -1.20 [-1.58, -0.83] |
| Pelham 1990a | 4.81 | 3.2 | 22 | 6.3 | 4.8 | 22 | 2.8% | -0.36 [-0.95, 0.24] |
| Pelham 1999 | 2.6 | 1.4 | 25 | 5.6 | 2.9 | 25 | 2.8% | -1.30 [-1.91, -0.68] |
| Pelham 2002 | 3 | 1.4 | 136 | 4.4 | 2.3 | 136 | 4.2% | -0.73 [-0.98, -0.49] |
| Pelham 2005 | 5.2 | 3.8 | 29 | 6.9 | 4.8 | 29 | 3.1% | -0.39 [-0.91, 0.13] |
| Pelham 2014 | 2.3 | 1.5 | 47 | 6 | 3.6 | 47 | 3.4% | -1.33 [-1.78, -0.88] |
| Silva 2005a | 0.67 | 0.58 | 54 | 1.94 | 1.18 | 54 | 3.5% | -1.36 [-1.78, -0.94] |
| Silva 2008 | 2.24 | 9.8542 | 68 | 7.77 | 9.7965 | 68 | 3.9% | -0.56 [-0.90, -0.22] |
| Solanto 2009 | 18.21 | 10.34 | 30 | 26.58 | 11.39 | 30 | 3.1% | -0.76 [-1.28, -0.23] |
| Swanson 2004b | 12.04 | 11.62 | 184 | 22.15 | 13.91 | 184 | 4.4% | -0.79 [-1.00, -0.58] |
| Wilens 2010 | 14.76 | 14.48 | 30 | 28.33 | 15.75 | 30 | 3.1% | -0.89 [-1.42, -0.35] |
| **Subtotal (95% CI)** | | | **1156** | | | **1152** | **60.8%** | **-0.95 [-1.13, -0.77]** |
| Heterogeneity: Tau² = 0.09; Chi² = 59.92, df = 17 (P < 0.00001); I² = 72% | | | | | | | | |
| Test for overall effect: Z = 10.59 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **2224** | | | **1991** | **100.0%** | **-0.83 [-0.98, -0.67]** |
| Heterogeneity: Tau² = 0.14; Chi² = 149.20, df = 27 (P < 0.00001); I² = 82% | | | | | | | | |
| Test for overall effect: Z = 10.26 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 4.00, df = 1 (P = 0.05), I² = 75.0% | | | | | | | | |




## 3 - Parent-rated ADHD symptoms

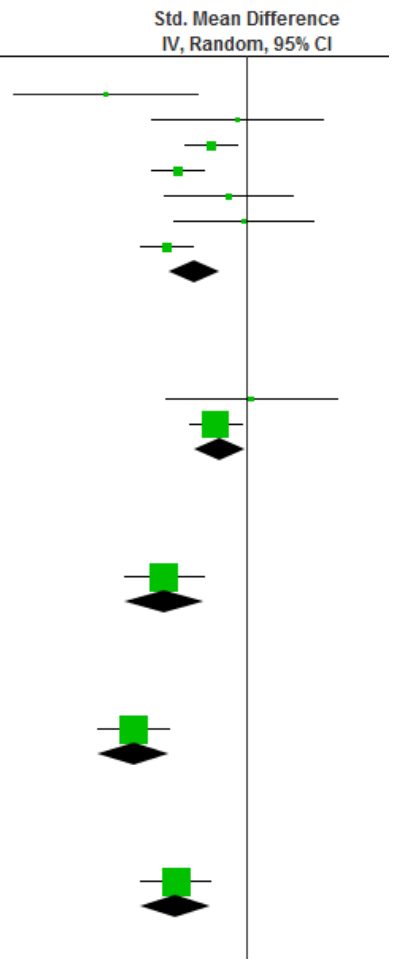
### 3.1 All parallel-group trials and first-period cross-over trials

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **3.1.1 Low risk of bias** | | | | | | | | |
| **Subtotal (95% CI)** | | | **0** | | | **0** | | **Not estimable** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | | |
| **3.1.2 High risk of bias** | | | | | | | | |
| Arnold 2004 | 0.8 | 0.7 | 35 | 1.3 | 0.9 | 40 | 4.9% | -0.61 [-1.07, -0.14] |
| Brown 1985 | 7.5 | 2.6 | 10 | 13.1 | 4.1 | 10 | 1.8% | -1.56 [-2.59, -0.53] |
| Carlson 2007 | -3.3 | 20.9 | 9 | -4.3 | 5.2 | 8 | 2.0% | 0.06 [-0.89, 1.01] |
| Childress 2009 | 19.6 | 12.75 | 57 | 35.9 | 13.01 | 63 | 5.6% | -1.26 [-1.65, -0.86] |
| Duric 2012 | 23.7 | 15.153 | 22 | 26.7 | 13.02 | 19 | 3.7% | -0.21 [-0.82, 0.41] |
| Findling 2006 | 5.1 | 2.9321 | 120 | 8.1 | 3.0232 | 39 | 5.8% | -1.01 [-1.39, -0.63] |
| Findling 2008 | 28.4 | 21.07 | 94 | 37 | 23.39 | 88 | 6.8% | -0.39 [-0.68, -0.09] |
| Findling 2010 | 36.52 | 17.6537 | 143 | 50 | 17.6537 | 72 | 6.8% | -0.76 [-1.05, -0.47] |
| Firestone 1981 | 13.5 | 7.26 | 18 | 14.9 | 6.58 | 13 | 3.0% | -0.20 [-0.91, 0.52] |
| Ialongo 1994 | 9.76 | 5.94 | 13 | 9.9 | 4.28 | 12 | 2.7% | -0.03 [-0.81, 0.76] |
| Jensen 1999 (MTA) | 0.85 | 0.63 | 133 | 1.24 | 0.72 | 129 | 7.3% | -0.58 [-0.82, -0.33] |
| Kollins 2006 (PATS) | 1.09 | 0.72 | 48 | 1.41 | 0.77 | 38 | 5.3% | -0.43 [-0.86, 0.00] |
| Lehmkuhl 2002 | 1.1 | 0.6557 | 43 | 1.7 | 0.6481 | 42 | 5.1% | -0.91 [-1.36, -0.46] |
| Newcorn 2008 | -10.2 | 9.1 | 195 | -2.3 | 8.4 | 66 | 6.8% | -0.88 [-1.17, -0.59] |
| Schachar 1997a | 1.2 | 0.7 | 37 | 1.3 | 0.7 | 29 | 4.7% | -0.14 [-0.63, 0.35] |
| Szobot 2004 | 11.9 | 6.1 | 19 | 16.4 | 6.2 | 17 | 3.3% | -0.72 [-1.39, -0.04] |
| Taylor 1987 | 0.36 | 0.42 | 39 | 0.68 | 0.64 | 39 | 5.0% | -0.59 [-1.04, -0.13] |
| Tucker 2009 | -8.2 | 6.05 | 53 | -3.2 | 4.6 | 56 | 5.6% | -0.93 [-1.32, -0.53] |
| Wilens 2006b | 16.65 | 11.07 | 87 | 20.84 | 13.58 | 90 | 6.7% | -0.34 [-0.63, -0.04] |
| Wolraich 2001 | 5.44 | 3.22 | 81 | 9.48 | 3.78 | 46 | 5.7% | -1.17 [-1.56, -0.78] |
| Zeni 2009 | 1.2022 | 0.65764 | 9 | 1.9317 | 0.69847 | 6 | 1.6% | -1.02 [-2.14, 0.10] |
| **Subtotal (95% CI)** | | | **1265** | | | **922** | **100.0%** | **-0.66 [-0.82, -0.51]** |
| Heterogeneity: Tau² = 0.07; Chi² = 50.14, df = 20 (P = 0.0002); I² = 60% | | | | | | | | |
| Test for overall effect: Z = 8.51 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **1265** | | | **922** | **100.0%** | **-0.66 [-0.82, -0.51]** |
| Heterogeneity: Tau² = 0.07; Chi² = 50.14, df = 20 (P = 0.0002); I² = 60% | | | | | | | | |
| Test for overall effect: Z = 8.51 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | |




### 3.2 Subgroup analysis: types of scales

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **3.2.1 Conners' Parent Rating Scale (CPRS)** | | | | | | | | |
| Brown 1985 | 7.5 | 2.6 | 10 | 13.1 | 4.1 | 10 | 6.1% | -1.56 [-2.59, -0.53] |
| Carlson 2007 | -4.7 | 24.5 | 9 | -2.9 | 5.6 | 8 | 6.9% | -0.09 [-1.05, 0.86] |
| Findling 2008 | 28.4 | 21.07 | 94 | 37 | 23.39 | 88 | 22.5% | -0.39 [-0.68, -0.09] |
| Findling 2010 | 36.52 | 17.6537 | 143 | 50 | 17.6537 | 72 | 22.5% | -0.76 [-1.05, -0.47] |
| Firestone 1981 | 13.5 | 7.26 | 18 | 14.9 | 6.58 | 13 | 10.3% | -0.20 [-0.91, 0.52] |
| Ialongo 1994 | 9.76 | 5.94 | 13 | 9.9 | 4.28 | 12 | 9.1% | -0.03 [-0.81, 0.76] |
| Newcorn 2008 | -10.2 | 9.1 | 195 | -2.3 | 8.4 | 66 | 22.6% | -0.88 [-1.17, -0.59] |
| **Subtotal (95% CI)** | | | **482** | | | **269** | **100.0%** | **-0.58 [-0.87, -0.30]** |
| Heterogeneity: Tau² = 0.07; Chi² = 14.42, df = 6 (P = 0.03); I² = 58% | | | | | | | | |
| Test for overall effect: Z = 4.00 (P < 0.0001) | | | | | | | | |
| **3.2.2 ADHD Rating Scale - Fourth Edition (ADHD-RS-IV)** | | | | | | | | |
| Carlson 2007 | -3.3 | 20.9 | 9 | -4.3 | 5.2 | 8 | 8.8% | 0.06 [-0.89, 1.01] |
| Wilens 2006b | 16.65 | 11.07 | 87 | 20.84 | 13.58 | 90 | 91.2% | -0.34 [-0.63, -0.04] |
| **Subtotal (95% CI)** | | | **96** | | | **98** | **100.0%** | **-0.30 [-0.58, -0.02]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 1 (P = 0.44); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 2.08 (P = 0.04) | | | | | | | | |
| **3.2.3 Fremdbeurteilungsbogen für Hyperkinetische Störungen (FBB-HKS)** | | | | | | | | |
| Lehmkuhl 2002 | 1.1 | 0.6557 | 43 | 1.7 | 0.6481 | 42 | 100.0% | -0.91 [-1.36, -0.46] |
| **Subtotal (95% CI)** | | | **43** | | | **42** | **100.0%** | **-0.91 [-1.36, -0.46]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 3.99 (P < 0.0001) | | | | | | | | |
| **3.2.4 Conners' ADHD/DSM-IV Scales - Parent (CADS-P)** | | | | | | | | |
| Childress 2009 | 19.6 | 12.75 | 57 | 35.9 | 13.01 | 63 | 100.0% | -1.26 [-1.65, -0.86] |
| **Subtotal (95% CI)** | | | **57** | | | **63** | **100.0%** | **-1.26 [-1.65, -0.86]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 6.27 (P < 0.00001) | | | | | | | | |
| **3.2.5 CADS-P Inattentive subscale** | | | | | | | | |
| Tucker 2009 | -8.8 | 6.38 | 53 | -3.8 | 6.32 | 56 | 100.0% | -0.78 [-1.17, -0.39] |
| **Subtotal (95% CI)** | | | **53** | | | **56** | **100.0%** | **-0.78 [-1.17, -0.39]** |
| Heterogeneity: Not applicable | | | | | | | | |



Test for overall effect: Z = 3.93 (P < 0.0001)

**3.2.6 CADS-P Hyperactivity subscale**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Tucker 2009 | -8.2 | 6.05 | 53 | -3.2 | 4.6 | 56 | 100.0% | -0.93 [-1.32, -0.53] |
| **Subtotal (95% CI)** | | | **53** | | | **56** | **100.0%** | **-0.93 [-1.32, -0.53]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 4.59 (P < 0.00001)

**3.2.7 Clinican's Manual for the Assesment of Disruptive Behavior Disorders Rating Scale for Parents (Barkley)**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Duric 2012 | 23.7 | 15.153 | 22 | 26.7 | 13.02 | 19 | 100.0% | -0.21 [-0.82, 0.41] |
| **Subtotal (95% CI)** | | | **22** | | | **19** | **100.0%** | **-0.21 [-0.82, 0.41]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)

**3.2.8 Abbreviated Conners' Rating Scale (ACRS) - Parent**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Lehmkuhl 2002 | 10 | 6.5574 | 43 | 16 | 12.9615 | 42 | 70.8% | -0.58 [-1.02, -0.15] |
| Szobot 2004 | 11.9 | 6.1 | 19 | 16.4 | 6.2 | 17 | 29.2% | -0.72 [-1.39, -0.04] |
| **Subtotal (95% CI)** | | | **62** | | | **59** | **100.0%** | **-0.62 [-0.99, -0.25]** |

Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 3.32 (P = 0.0009)

**3.2.9 Swanson, Nolan, and Pelham, Fourth Edition - Parent (SNAP-IV-Parent) Scale**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Arnold 2004 | 0.8 | 0.7 | 35 | 1.3 | 0.9 | 40 | 17.4% | -0.61 [-1.07, -0.14] |
| Jensen 1999 (MTA) | 0.85 | 0.63 | 133 | 1.24 | 0.72 | 129 | 61.4% | -0.58 [-0.82, -0.33] |
| Taylor 1987 | 0.36 | 0.42 | 39 | 0.68 | 0.64 | 39 | 18.2% | -0.59 [-1.04, -0.13] |
| Zeni 2009 | 1.2022 | 0.65764 | 9 | 1.9317 | 0.69847 | 6 | 3.0% | -1.02 [-2.14, 0.10] |
| **Subtotal (95% CI)** | | | **216** | | | **214** | **100.0%** | **-0.60 [-0.79, -0.40]** |

Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 3 (P = 0.90); I² = 0%
Test for overall effect: Z = 6.03 (P < 0.00001)

**3.2.10 Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) Scale**

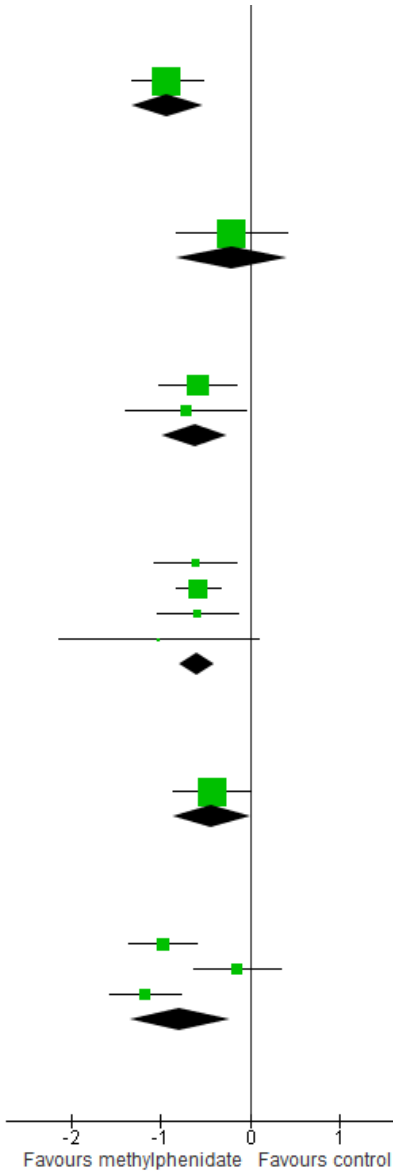
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Kollins 2006 (PATS) | 1.09 | 0.72 | 48 | 1.41 | 0.77 | 38 | 100.0% | -0.43 [-0.86, 0.00] |
| **Subtotal (95% CI)** | | | **48** | | | **38** | **100.0%** | **-0.43 [-0.86, 0.00]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.94 (P = 0.05)

**3.2.11 IOWA Conners' Rating Scale - Inattention/Overactivity (IOWA-I/O)**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Findling 2006 | 5.1 | 3.0672 | 120 | 8.1 | 3.06 | 39 | 34.5% | -0.97 [-1.35, -0.60] |
| Schachar 1997a | 1.2 | 0.7 | 37 | 1.3 | 0.7 | 29 | 31.3% | -0.14 [-0.63, 0.35] |
| Wolraich 2001 | 5.44 | 3.22 | 81 | 9.48 | 3.78 | 46 | 34.2% | -1.17 [-1.56, -0.78] |
| **Subtotal (95% CI)** | | | **238** | | | **114** | **100.0%** | **-0.78 [-1.35, -0.21]** |

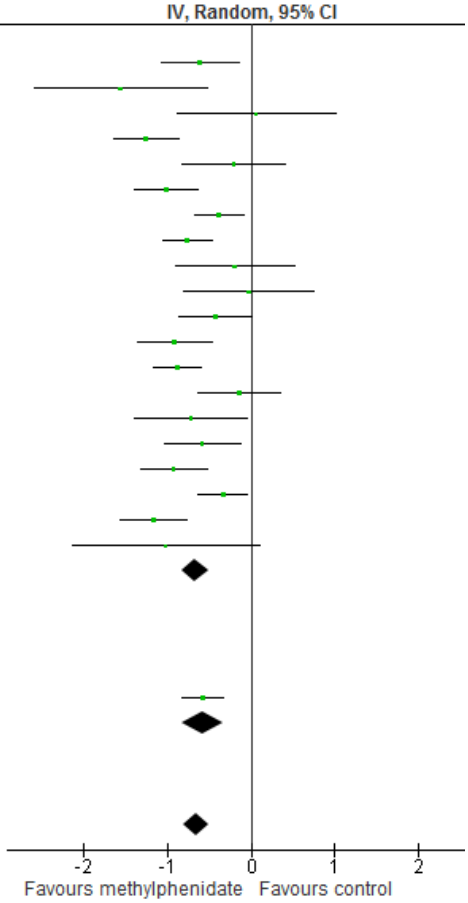
Heterogeneity: Tau² = 0.20; Chi² = 11.15, df = 2 (P = 0.004); I² = 82%
Test for overall effect: Z = 2.70 (P = 0.007)



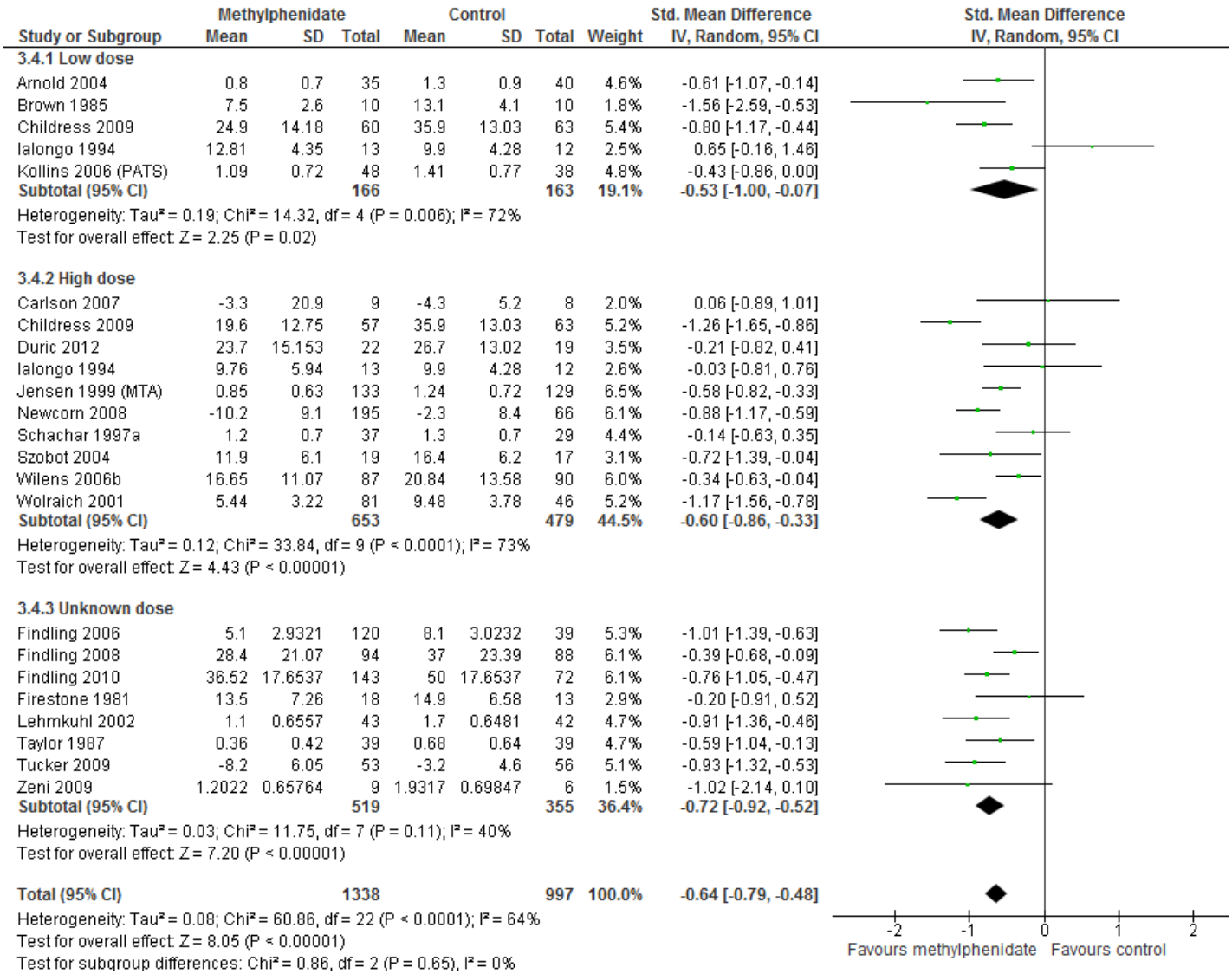

Test for subgroup differences: Chi² = 22.34, df = 10 (P = 0.01), I² = 55.2%

**3.3 Subgroup analysis: duration of treatment**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **3.3.1 Short term (up to 6 months)** | | | | | | | | |
| Arnold 2004 | 0.8 | 0.7 | 35 | 1.3 | 0.9 | 40 | 4.9% | -0.61 [-1.07, -0.14] |
| Brown 1985 | 7.5 | 2.6 | 10 | 13.1 | 4.1 | 10 | 1.8% | -1.56 [-2.59, -0.53] |
| Carlson 2007 | -3.3 | 20.9 | 9 | -4.3 | 5.2 | 8 | 2.0% | 0.06 [-0.89, 1.01] |
| Childress 2009 | 19.6 | 12.75 | 57 | 35.9 | 13.01 | 63 | 5.6% | -1.26 [-1.65, -0.86] |
| Duric 2012 | 23.7 | 15.153 | 22 | 26.7 | 13.02 | 19 | 3.7% | -0.21 [-0.82, 0.41] |
| Findling 2006 | 5.1 | 2.9321 | 120 | 8.1 | 3.0232 | 39 | 5.8% | -1.01 [-1.39, -0.63] |
| Findling 2008 | 28.4 | 21.07 | 94 | 37 | 23.39 | 88 | 6.8% | -0.39 [-0.68, -0.09] |
| Findling 2010 | 36.52 | 17.6537 | 143 | 50 | 17.6537 | 72 | 6.8% | -0.76 [-1.05, -0.47] |
| Firestone 1981 | 13.5 | 7.26 | 18 | 14.9 | 6.58 | 13 | 3.0% | -0.20 [-0.91, 0.52] |
| Ialongo 1994 | 9.76 | 5.94 | 13 | 9.9 | 4.28 | 12 | 2.7% | -0.03 [-0.81, 0.76] |
| Kollins 2006 (PATS) | 1.09 | 0.72 | 48 | 1.41 | 0.77 | 38 | 5.3% | -0.43 [-0.86, 0.00] |
| Lehmkuhl 2002 | 1.1 | 0.6557 | 43 | 1.7 | 0.6481 | 42 | 5.1% | -0.91 [-1.36, -0.46] |
| Newcorn 2008 | -10.2 | 9.1 | 195 | -2.3 | 8.4 | 66 | 6.8% | -0.88 [-1.17, -0.59] |
| Schachar 1997a | 1.2 | 0.7 | 37 | 1.3 | 0.7 | 29 | 4.7% | -0.14 [-0.63, 0.35] |
| Szobot 2004 | 11.9 | 6.1 | 19 | 16.4 | 6.2 | 17 | 3.3% | -0.72 [-1.39, -0.04] |
| Taylor 1987 | 0.36 | 0.42 | 39 | 0.68 | 0.64 | 39 | 5.0% | -0.59 [-1.04, -0.13] |
| Tucker 2009 | -8.2 | 6.05 | 53 | -3.2 | 4.6 | 56 | 5.6% | -0.93 [-1.32, -0.53] |
| Wilens 2006b | 16.65 | 11.07 | 87 | 20.84 | 13.58 | 90 | 6.7% | -0.34 [-0.63, -0.04] |
| Wolraich 2001 | 5.44 | 3.22 | 81 | 9.48 | 3.78 | 46 | 5.7% | -1.17 [-1.56, -0.78] |
| Zeni 2009 | 1.2022 | 0.65764 | 9 | 1.9317 | 0.69847 | 6 | 1.6% | -1.02 [-2.14, 0.10] |
| **Subtotal (95% CI)** | | | **1132** | | | **793** | **92.7%** | **-0.67 [-0.84, -0.50]** |
| Heterogeneity: Tau² = 0.08; Chi² = 49.47, df = 19 (P = 0.0002); I² = 62% | | | | | | | | |
| Test for overall effect: Z = 7.89 (P < 0.00001) | | | | | | | | |
| **3.3.2 Long term (over 6 months)** | | | | | | | | |
| Jensen 1999 (MTA) | 0.85 | 0.63 | 133 | 1.24 | 0.72 | 129 | 7.3% | -0.58 [-0.82, -0.33] |
| **Subtotal (95% CI)** | | | **133** | | | **129** | **7.3%** | **-0.58 [-0.82, -0.33]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 4.56 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **1265** | | | **922** | **100.0%** | **-0.66 [-0.82, -0.51]** |
| Heterogeneity: Tau² = 0.07; Chi² = 50.14, df = 20 (P = 0.0002); I² = 60% | | | | | | | | |
| Test for overall effect: Z = 8.51 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.39, df = 1 (P = 0.53), I² = 0% | | | | | | | | |



### 3.4 Subgroup analysis: dose



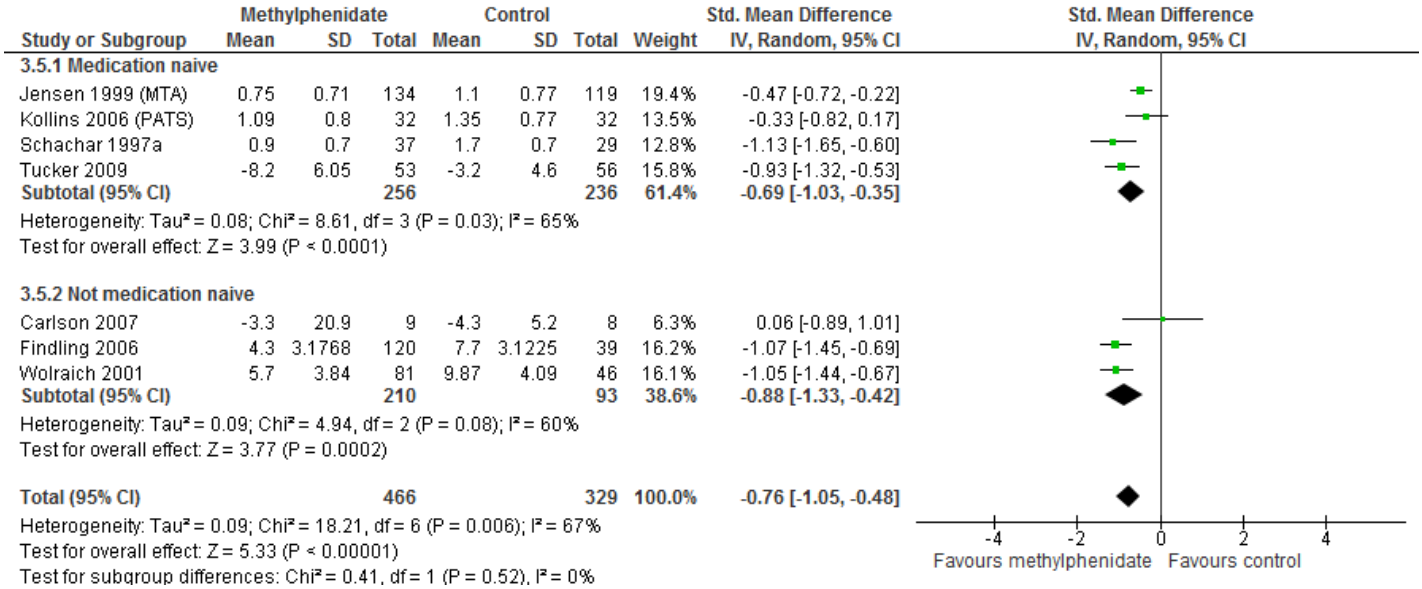
| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **3.4.1 Low dose** | | | | | | | | |
| Arnold 2004 | 0.8 | 0.7 | 35 | 1.3 | 0.9 | 40 | 4.6% | -0.61 [-1.07, -0.14] |
| Brown 1985 | 7.5 | 2.6 | 10 | 13.1 | 4.1 | 10 | 1.8% | -1.56 [-2.59, -0.53] |
| Childress 2009 | 24.9 | 14.18 | 60 | 35.9 | 13.03 | 63 | 5.4% | -0.80 [-1.17, -0.44] |
| Ialongo 1994 | 12.81 | 4.35 | 13 | 9.9 | 4.28 | 12 | 2.5% | 0.65 [-0.16, 1.46] |
| Kollins 2006 (PATS) | 1.09 | 0.72 | 48 | 1.41 | 0.77 | 38 | 4.8% | -0.43 [-0.86, 0.00] |
| **Subtotal (95% CI)** | | | **166** | | | **163** | **19.1%** | **-0.53 [-1.00, -0.07]** |
| Heterogeneity: Tau² = 0.19; Chi² = 14.32, df = 4 (P = 0.006); I² = 72% | | | | | | | | |
| Test for overall effect: Z = 2.25 (P = 0.02) | | | | | | | | |
| **3.4.2 High dose** | | | | | | | | |
| Carlson 2007 | -3.3 | 20.9 | 9 | -4.3 | 5.2 | 8 | 2.0% | 0.06 [-0.89, 1.01] |
| Childress 2009 | 19.6 | 12.75 | 57 | 35.9 | 13.03 | 63 | 5.2% | -1.26 [-1.65, -0.86] |
| Duric 2012 | 23.7 | 15.153 | 22 | 26.7 | 13.02 | 19 | 3.5% | -0.21 [-0.82, 0.41] |
| Ialongo 1994 | 9.76 | 5.94 | 13 | 9.9 | 4.28 | 12 | 2.6% | -0.03 [-0.81, 0.76] |
| Jensen 1999 (MTA) | 0.85 | 0.63 | 133 | 1.24 | 0.72 | 129 | 6.5% | -0.58 [-0.82, -0.33] |
| Newcorn 2008 | -10.2 | 9.1 | 195 | -2.3 | 8.4 | 66 | 6.1% | -0.88 [-1.17, -0.59] |
| Schachar 1997a | 1.2 | 0.7 | 37 | 1.3 | 0.7 | 29 | 4.4% | -0.14 [-0.63, 0.35] |
| Szobot 2004 | 11.9 | 6.1 | 19 | 16.4 | 6.2 | 17 | 3.1% | -0.72 [-1.39, -0.04] |
| Wilens 2006b | 16.65 | 11.07 | 87 | 20.84 | 13.58 | 90 | 6.0% | -0.34 [-0.63, -0.04] |
| Wolraich 2001 | 5.44 | 3.22 | 81 | 9.48 | 3.78 | 46 | 5.2% | -1.17 [-1.56, -0.78] |
| **Subtotal (95% CI)** | | | **653** | | | **479** | **44.5%** | **-0.60 [-0.86, -0.33]** |
| Heterogeneity: Tau² = 0.12; Chi² = 33.84, df = 9 (P < 0.0001); I² = 73% | | | | | | | | |
| Test for overall effect: Z = 4.43 (P < 0.00001) | | | | | | | | |
| **3.4.3 Unknown dose** | | | | | | | | |
| Findling 2006 | 5.1 | 2.9321 | 120 | 8.1 | 3.0232 | 39 | 5.3% | -1.01 [-1.39, -0.63] |
| Findling 2008 | 28.4 | 21.07 | 94 | 37 | 23.39 | 88 | 6.1% | -0.39 [-0.68, -0.09] |
| Findling 2010 | 36.52 | 17.6537 | 143 | 50 | 17.6537 | 72 | 6.1% | -0.76 [-1.05, -0.47] |
| Firestone 1981 | 13.5 | 7.26 | 18 | 14.9 | 6.58 | 13 | 2.9% | -0.20 [-0.91, 0.52] |
| Lehmkuhl 2002 | 1.1 | 0.6557 | 43 | 1.7 | 0.6481 | 42 | 4.7% | -0.91 [-1.36, -0.46] |
| Taylor 1987 | 0.36 | 0.42 | 39 | 0.68 | 0.64 | 39 | 4.7% | -0.59 [-1.04, -0.13] |
| Tucker 2009 | -8.2 | 6.05 | 53 | -3.2 | 4.6 | 56 | 5.1% | -0.93 [-1.32, -0.53] |
| Zeni 2009 | 1.2022 | 0.65764 | 9 | 1.9317 | 0.69847 | 6 | 1.5% | -1.02 [-2.14, 0.10] |
| **Subtotal (95% CI)** | | | **519** | | | **355** | **36.4%** | **-0.72 [-0.92, -0.52]** |
| Heterogeneity: Tau² = 0.03; Chi² = 11.75, df = 7 (P = 0.11); I² = 40% | | | | | | | | |
| Test for overall effect: Z = 7.20 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **1338** | | | **997** | **100.0%** | **-0.64 [-0.79, -0.48]** |
| Heterogeneity: Tau² = 0.08; Chi² = 60.86, df = 22 (P < 0.0001); I² = 64% | | | | | | | | |
| Test for overall effect: Z = 8.05 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.86, df = 2 (P = 0.65), I² = 0% | | | | | | | | |

Std. Mean Difference IV, Random, 95% CI

-2 -1 0 1 2

Favours methylphenidate Favours control

### 3.5 Medication status: medication naive versus not medication naive



| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **3.5.1 Medication naive** | | | | | | | | |
| Jensen 1999 (MTA) | 0.75 | 0.71 | 134 | 1.1 | 0.77 | 119 | 19.4% | -0.47 [-0.72, -0.22] |
| Kollins 2006 (PATS) | 1.09 | 0.8 | 32 | 1.35 | 0.77 | 32 | 13.5% | -0.33 [-0.82, 0.17] |
| Schachar 1997a | 0.9 | 0.7 | 37 | 1.7 | 0.7 | 29 | 12.8% | -1.13 [-1.65, -0.60] |
| Tucker 2009 | -8.2 | 6.05 | 53 | -3.2 | 4.6 | 56 | 15.8% | -0.93 [-1.32, -0.53] |
| **Subtotal (95% CI)** | | | **256** | | | **236** | **61.4%** | **-0.69 [-1.03, -0.35]** |
| Heterogeneity: Tau² = 0.08; Chi² = 8.61, df = 3 (P = 0.03); I² = 65% | | | | | | | | |
| Test for overall effect: Z = 3.99 (P < 0.0001) | | | | | | | | |
| **3.5.2 Not medication naive** | | | | | | | | |
| Carlson 2007 | -3.3 | 20.9 | 9 | -4.3 | 5.2 | 8 | 6.3% | 0.06 [-0.89, 1.01] |
| Findling 2006 | 4.3 | 3.1768 | 120 | 7.7 | 3.1225 | 39 | 16.2% | -1.07 [-1.45, -0.69] |
| Wolraich 2001 | 5.7 | 3.84 | 81 | 9.87 | 4.09 | 46 | 16.1% | -1.05 [-1.44, -0.67] |
| **Subtotal (95% CI)** | | | **210** | | | **93** | **38.6%** | **-0.88 [-1.33, -0.42]** |
| Heterogeneity: Tau² = 0.09; Chi² = 4.94, df = 2 (P = 0.08); I² = 60% | | | | | | | | |
| Test for overall effect: Z = 3.77 (P = 0.0002) | | | | | | | | |
| **Total (95% CI)** | | | **466** | | | **329** | **100.0%** | **-0.76 [-1.05, -0.48]** |
| Heterogeneity: Tau² = 0.09; Chi² = 18.21, df = 6 (P = 0.006); I² = 67% | | | | | | | | |
| Test for overall effect: Z = 5.33 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.41, df = 1 (P = 0.52), I² = 0% | | | | | | | | |

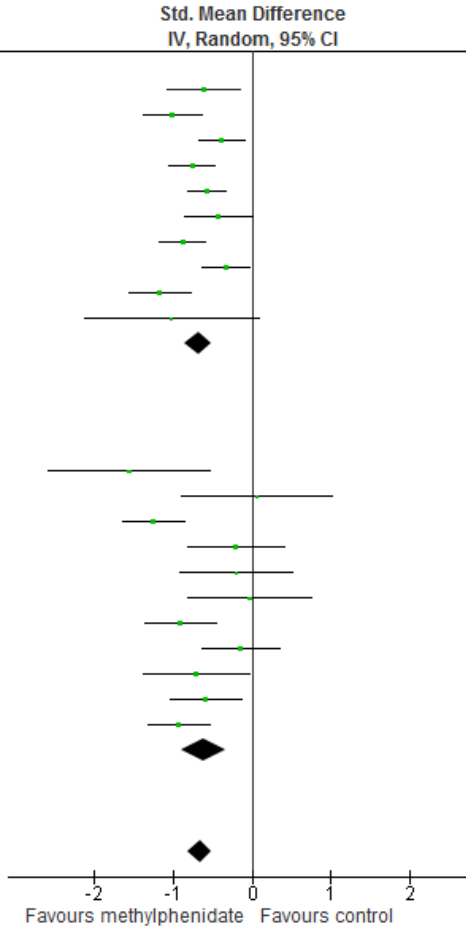
Std. Mean Difference IV, Random, 95% CI

-4 -2 0 2 4

Favours methylphenidate Favours control

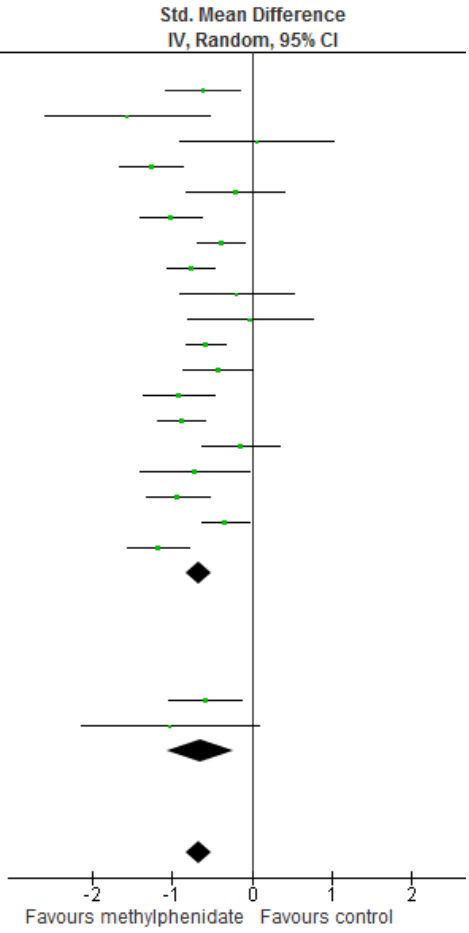
### 3.6 Subgroup analysis: trials with cohort selection bias of all participants compared with trials without cohort selection bias of all participants

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **3.6.1 Trials with selection bias of all participants** | | | | | | | | |
| Arnold 2004 | 0.8 | 0.7 | 35 | 1.3 | 0.9 | 40 | 4.9% | -0.61 [-1.07, -0.14] |
| Findling 2006 | 5.1 | 2.9321 | 120 | 8.1 | 3.0232 | 39 | 5.8% | -1.01 [-1.39, -0.63] |
| Findling 2008 | 28.4 | 21.07 | 94 | 37 | 23.39 | 88 | 6.8% | -0.39 [-0.68, -0.09] |
| Findling 2010 | 36.52 | 17.6537 | 143 | 50 | 17.6537 | 72 | 6.8% | -0.76 [-1.05, -0.47] |
| Jensen 1999 (MTA) | 0.85 | 0.63 | 133 | 1.24 | 0.72 | 129 | 7.3% | -0.58 [-0.82, -0.33] |
| Kollins 2006 (PATS) | 1.09 | 0.72 | 48 | 1.41 | 0.77 | 38 | 5.3% | -0.43 [-0.86, 0.00] |
| Newcorn 2008 | -10.2 | 9.1 | 195 | -2.3 | 8.4 | 66 | 6.8% | -0.88 [-1.17, -0.59] |
| Wilens 2006b | 16.65 | 11.07 | 87 | 20.84 | 13.58 | 90 | 6.7% | -0.34 [-0.63, -0.04] |
| Wolraich 2001 | 5.44 | 3.22 | 81 | 9.48 | 3.78 | 46 | 5.7% | -1.17 [-1.56, -0.78] |
| Zeni 2009 | 1.2022 | 0.65764 | 9 | 1.9317 | 0.69847 | 6 | 1.6% | -1.02 [-2.14, 0.10] |
| **Subtotal (95% CI)** | | | **945** | | | **614** | **57.5%** | **-0.68 [-0.86, -0.51]** |
| Heterogeneity: Tau² = 0.05; Chi² = 22.53, df = 9 (P = 0.007); I² = 60% | | | | | | | | |
| Test for overall effect: Z = 7.53 (P < 0.00001) | | | | | | | | |
| **3.6.2 Trials without cohort selection bias of all participants** | | | | | | | | |
| Brown 1985 | 7.5 | 2.6 | 10 | 13.1 | 4.1 | 10 | 1.8% | -1.56 [-2.59, -0.53] |
| Carlson 2007 | -3.3 | 20.9 | 9 | -4.3 | 5.2 | 8 | 2.0% | 0.06 [-0.89, 1.01] |
| Childress 2009 | 19.6 | 12.75 | 57 | 35.9 | 13.01 | 63 | 5.6% | -1.26 [-1.65, -0.86] |
| Duric 2012 | 23.7 | 15.153 | 22 | 26.7 | 13.02 | 19 | 3.7% | -0.21 [-0.82, 0.41] |
| Firestone 1981 | 13.5 | 7.26 | 18 | 14.9 | 6.58 | 13 | 3.0% | -0.20 [-0.91, 0.52] |
| Ialongo 1994 | 9.76 | 5.94 | 13 | 9.9 | 4.28 | 12 | 2.7% | -0.03 [-0.81, 0.76] |
| Lehmkuhl 2002 | 1.1 | 0.6557 | 43 | 1.7 | 0.6481 | 42 | 5.1% | -0.91 [-1.36, -0.46] |
| Schachar 1997a | 1.2 | 0.7 | 37 | 1.3 | 0.7 | 29 | 4.7% | -0.14 [-0.63, 0.35] |
| Szobot 2004 | 11.9 | 6.1 | 19 | 16.4 | 6.2 | 17 | 3.3% | -0.72 [-1.39, -0.04] |
| Taylor 1987 | 0.36 | 0.42 | 39 | 0.68 | 0.64 | 39 | 5.0% | -0.59 [-1.04, -0.13] |
| Tucker 2009 | -8.2 | 6.05 | 53 | -3.2 | 4.6 | 56 | 5.6% | -0.93 [-1.32, -0.53] |
| **Subtotal (95% CI)** | | | **320** | | | **308** | **42.5%** | **-0.62 [-0.90, -0.33]** |
| Heterogeneity: Tau² = 0.14; Chi² = 27.50, df = 10 (P = 0.002); I² = 64% | | | | | | | | |
| Test for overall effect: Z = 4.21 (P < 0.0001) | | | | | | | | |
| **Total (95% CI)** | | | **1265** | | | **922** | **100.0%** | **-0.66 [-0.82, -0.51]** |
| Heterogeneity: Tau² = 0.07; Chi² = 50.14, df = 20 (P = 0.0002); I² = 60% | | | | | | | | |
| Test for overall effect: Z = 8.51 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.16, df = 1 (P = 0.69), I² = 0% | | | | | | | | |



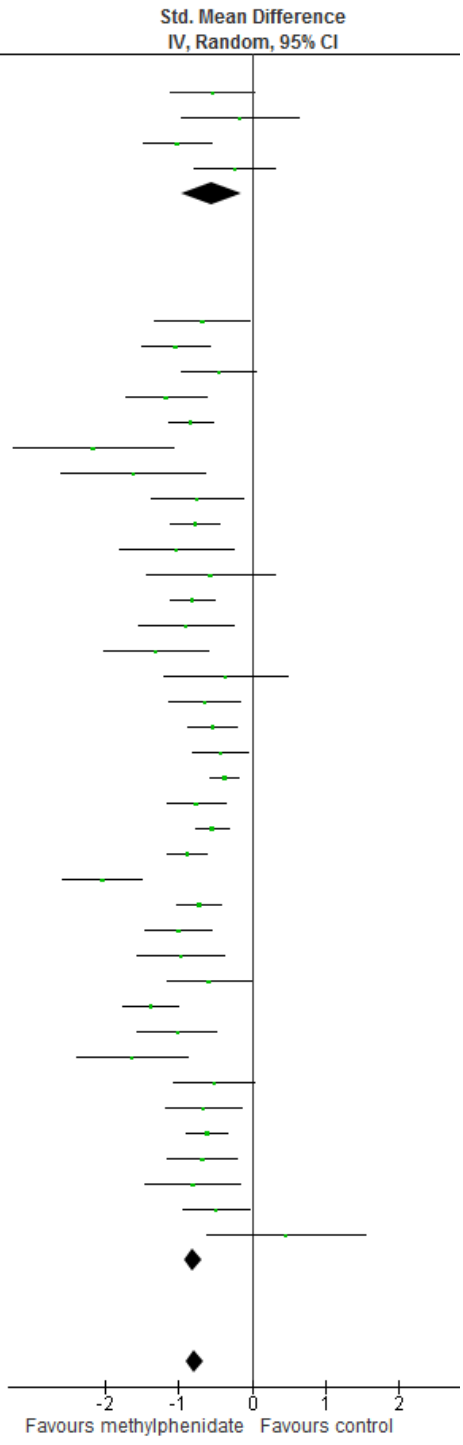

### 3.7 Subgroup analysis: parallel-group trials compared with first-period cross-over trials

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **3.7.1 Parallel-group trials** | | | | | | | | |
| Arnold 2004 | 0.8 | 0.7 | 35 | 1.3 | 0.9 | 40 | 4.9% | -0.61 [-1.07, -0.14] |
| Brown 1985 | 7.5 | 2.6 | 10 | 13.1 | 4.1 | 10 | 1.8% | -1.56 [-2.59, -0.53] |
| Carlson 2007 | -3.3 | 20.9 | 9 | -4.3 | 5.2 | 8 | 2.0% | 0.06 [-0.89, 1.01] |
| Childress 2009 | 19.6 | 12.75 | 57 | 35.9 | 13.01 | 63 | 5.6% | -1.26 [-1.65, -0.86] |
| Duric 2012 | 23.7 | 15.153 | 22 | 26.7 | 13.02 | 19 | 3.7% | -0.21 [-0.82, 0.41] |
| Findling 2006 | 5.1 | 2.9321 | 120 | 8.1 | 3.0232 | 39 | 5.8% | -1.01 [-1.39, -0.63] |
| Findling 2008 | 28.4 | 21.07 | 94 | 37 | 23.39 | 88 | 6.8% | -0.39 [-0.68, -0.09] |
| Findling 2010 | 36.52 | 17.6537 | 143 | 50 | 17.6537 | 72 | 6.8% | -0.76 [-1.05, -0.47] |
| Firestone 1981 | 13.5 | 7.26 | 18 | 14.9 | 6.58 | 13 | 3.0% | -0.20 [-0.91, 0.52] |
| Ialongo 1994 | 9.76 | 5.94 | 13 | 9.9 | 4.28 | 12 | 2.7% | -0.03 [-0.81, 0.76] |
| Jensen 1999 (MTA) | 0.85 | 0.63 | 133 | 1.24 | 0.72 | 129 | 7.3% | -0.58 [-0.82, -0.33] |
| Kollins 2006 (PATS) | 1.09 | 0.72 | 48 | 1.41 | 0.77 | 38 | 5.3% | -0.43 [-0.86, 0.00] |
| Lehmkuhl 2002 | 1.1 | 0.6557 | 43 | 1.7 | 0.6481 | 42 | 5.1% | -0.91 [-1.36, -0.46] |
| Newcorn 2008 | -10.2 | 9.1 | 195 | -2.3 | 8.4 | 66 | 6.8% | -0.88 [-1.17, -0.59] |
| Schachar 1997a | 1.2 | 0.7 | 37 | 1.3 | 0.7 | 29 | 4.7% | -0.14 [-0.63, 0.35] |
| Szobot 2004 | 11.9 | 6.1 | 19 | 16.4 | 6.2 | 17 | 3.3% | -0.72 [-1.39, -0.04] |
| Tucker 2009 | -8.2 | 6.05 | 53 | -3.2 | 4.6 | 56 | 5.6% | -0.93 [-1.32, -0.53] |
| Wilens 2006b | 16.65 | 11.07 | 87 | 20.84 | 13.58 | 90 | 6.7% | -0.34 [-0.63, -0.04] |
| Wolraich 2001 | 5.44 | 3.22 | 81 | 9.48 | 3.78 | 46 | 5.7% | -1.17 [-1.56, -0.78] |
| **Subtotal (95% CI)** | | | **1217** | | | **877** | **93.4%** | **-0.66 [-0.83, -0.50]** |
| Heterogeneity: Tau² = 0.07; Chi² = 49.63, df = 18 (P < 0.0001); I² = 64% | | | | | | | | |
| Test for overall effect: Z = 7.94 (P < 0.00001) | | | | | | | | |
| **3.7.2 First-period cross-over trials** | | | | | | | | |
| Taylor 1987 | 0.36 | 0.42 | 39 | 0.68 | 0.64 | 39 | 5.0% | -0.59 [-1.04, -0.13] |
| Zeni 2009 | 1.2022 | 0.65764 | 9 | 1.9317 | 0.69847 | 6 | 1.6% | -1.02 [-2.14, 0.10] |
| **Subtotal (95% CI)** | | | **48** | | | **45** | **6.6%** | **-0.65 [-1.07, -0.23]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 1 (P = 0.48); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 3.02 (P = 0.003) | | | | | | | | |
| **Total (95% CI)** | | | **1265** | | | **922** | **100.0%** | **-0.66 [-0.82, -0.51]** |
| Heterogeneity: Tau² = 0.07; Chi² = 50.14, df = 20 (P = 0.0002); I² = 60% | | | | | | | | |
| Test for overall effect: Z = 8.51 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0% | | | | | | | | |



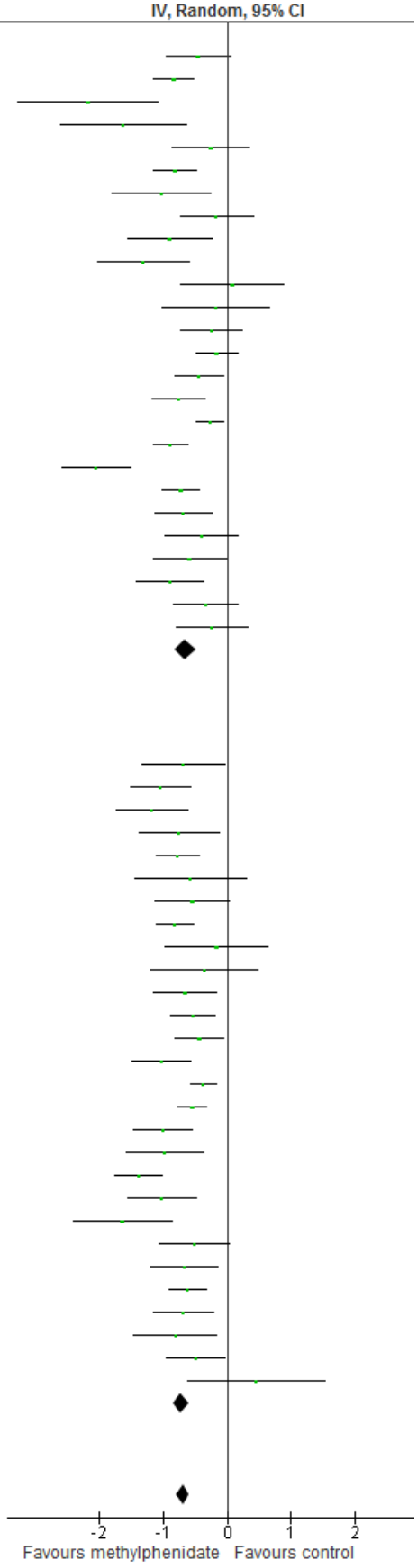
**3.8 ADHD symptoms, cross-over trials (endpoint data)**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **3.8.1 Low risk of bias** | | | | | | | | |
| DuPaul 1996 | 15.75 | 9.76 | 24 | 21 | 9.28 | 24 | 2.1% | -0.54 [-1.12, 0.03] |
| Flapper 2008 | 13 | 11.707 | 12 | 14.857 | 10.669 | 12 | 1.4% | -0.16 [-0.96, 0.64] |
| Gorman 2006 | 0.72 | 0.8324 | 41 | 1.61 | 0.8964 | 41 | 2.7% | -1.02 [-1.48, -0.56] |
| Stein 1996 | 5.5 | 3.1 | 25 | 6.3 | 3.5 | 25 | 2.2% | -0.24 [-0.79, 0.32] |
| **Subtotal (95% CI)** | | | **102** | | | **102** | **8.5%** | **-0.54 [-0.96, -0.13]** |
| Heterogeneity: Tau² = 0.09; Chi² = 5.99, df = 3 (P = 0.11); I² = 50% | | | | | | | | |
| Test for overall effect: Z = 2.59 (P = 0.010) | | | | | | | | |
| **3.8.2 High risk of bias** | | | | | | | | |
| Abikoff 2009 | 0.99 | 0.55 | 19 | 1.4 | 0.63 | 19 | 1.8% | -0.68 [-1.33, -0.02] |
| Barkley 1991 | 14.53 | 8.2 | 40 | 24.88 | 11.26 | 40 | 2.6% | -1.04 [-1.51, -0.57] |
| Barkley 2000 | 16.8 | 9.7 | 31 | 21.9 | 12.5 | 31 | 2.5% | -0.45 [-0.95, 0.05] |
| Blum 2011 | 64.8 | 26.5 | 30 | 89.6 | 13.1 | 30 | 2.3% | -1.17 [-1.72, -0.62] |
| Brams 2008 | -16.382 | 14.0495 | 86 | -4.622 | 14.0495 | 86 | 3.5% | -0.83 [-1.15, -0.52] |
| Brown 1984a | 11 | 3.49 | 11 | 19.55 | 4.08 | 11 | 0.9% | -2.17 [-3.26, -1.07] |
| Brown 1988 | 31.5 | 5.85 | 11 | 39.66 | 3.61 | 11 | 1.0% | -1.61 [-2.60, -0.63] |
| Chronis 2003 | 1.8 | 1.5 | 21 | 3.1 | 1.9 | 21 | 1.9% | -0.75 [-1.37, -0.12] |
| Coghill 2007 | 67 | 14.8 | 75 | 77.2 | 11.1 | 75 | 3.4% | -0.78 [-1.11, -0.44] |
| Cook 1993 | 0.41 | 0.175 | 15 | 0.59 | 0.166 | 15 | 1.5% | -1.03 [-1.79, -0.26] |
| Corkum 2008 | 62.14 | 14.11 | 10 | 69.38 | 10.23 | 11 | 1.2% | -0.57 [-1.45, 0.31] |
| Epstein 2011 | 19.6 | 10.09 | 93 | 28.26 | 11.12 | 93 | 3.6% | -0.81 [-1.11, -0.51] |
| Findling 2007 | 20.81 | 9.79 | 20 | 32.19 | 14.61 | 20 | 1.9% | -0.90 [-1.55, -0.24] |
| Fitzpatrick 1992a | 0.96 | 0.5 | 19 | 1.75 | 0.67 | 19 | 1.7% | -1.31 [-2.02, -0.60] |
| Gadow 1990 | 8.3 | 6.19 | 11 | 11 | 8.24 | 11 | 1.3% | -0.36 [-1.20, 0.49] |
| Gadow 1995 | 7.8 | 4.6 | 34 | 11.8 | 7.3 | 34 | 2.5% | -0.65 [-1.14, -0.16] |
| Gadow 2007 | 7.8 | 4.7 | 71 | 11 | 7 | 71 | 3.4% | -0.53 [-0.87, -0.20] |
| Gadow 2011 | 8.6 | 5.6 | 54 | 11.5 | 7.7 | 54 | 3.1% | -0.43 [-0.81, -0.05] |
| Grizenko 2012 | 56.76 | 11.87 | 198 | 61.64 | 14.19 | 198 | 4.2% | -0.37 [-0.57, -0.17] |
| Hoeppner 1997 | 7.13 | 6.37 | 50 | 12.16 | 6.78 | 50 | 3.0% | -0.76 [-1.17, -0.35] |
| Kollins 2006 (PATS) | 1.09 | 0.69 | 142 | 1.47 | 0.7 | 165 | 4.0% | -0.55 [-0.77, -0.32] |
| Manos 1999 | 10.1 | 6.71 | 117 | 18.61 | 11.86 | 117 | 3.8% | -0.88 [-1.15, -0.61] |
| McBride 1988a | 6.5 | 3.9 | 41 | 17.4 | 6.4 | 41 | 2.3% | -2.04 [-2.58, -1.50] |
| McGough 2006 | 20.2 | 20.3481 | 93 | 35.3 | 21.3125 | 93 | 3.6% | -0.72 [-1.02, -0.42] |
| Musten 1997 | 63.29 | 13.44 | 41 | 77.23 | 14.1 | 41 | 2.7% | -1.00 [-1.46, -0.54] |
| Pearson 2013 | 55.8 | 9.3 | 24 | 66.8 | 12.7 | 24 | 2.0% | -0.97 [-1.57, -0.37] |
| Pelham 1999 | 1.7 | 1.5 | 25 | 3 | 2.7 | 25 | 2.2% | -0.59 [-1.15, -0.02] |
| Pelham 2001a | 11.41 | 6.23 | 68 | 19.91 | 6.02 | 68 | 3.2% | -1.38 [-1.75, -1.00] |
| Pelham 2005 | 2.3 | 2.2 | 30 | 5.5 | 3.8 | 30 | 2.3% | -1.02 [-1.56, -0.48] |
| Schachar 2008 | -0.98 | 2.14 | 18 | 3.2 | 2.82 | 18 | 1.5% | -1.63 [-2.40, -0.87] |
| Smithee 1998 | 0.8639 | 0.4415 | 26 | 1.141 | 0.61022 | 26 | 2.2% | -0.51 [-1.07, 0.04] |
| Solanto 2009 | 56.96 | 12.41 | 30 | 65.8 | 13.98 | 30 | 2.4% | -0.66 [-1.18, -0.14] |
| Stein 2011 | 20.27 | 13.557 | 93 | 29.12 | 15.077 | 101 | 3.7% | -0.61 [-0.90, -0.33] |
| Taylor 1987 | 0.38 | 0.46 | 37 | 0.81 | 0.76 | 37 | 2.6% | -0.68 [-1.15, -0.21] |
| Tirosh 1993a | 10.75 | 2.9 | 20 | 14 | 4.8 | 20 | 1.9% | -0.80 [-1.45, -0.16] |
| Zeiner 1999 | 3.08 | 3.7 | 38 | 5.25 | 5.01 | 38 | 2.7% | -0.49 [-0.94, -0.03] |
| Zeni 2009 | 1.6267 | 0.6894 | 6 | 1.2625 | 0.77765 | 8 | 0.9% | 0.46 [-0.62, 1.54] |
| **Subtotal (95% CI)** | | | **1748** | | | **1782** | **91.5%** | **-0.81 [-0.92, -0.69]** |
| Heterogeneity: Tau² = 0.07; Chi² = 90.11, df = 36 (P < 0.00001); I² = 60% | | | | | | | | |
| Test for overall effect: Z = 13.27 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **1850** | | | **1884** | **100.0%** | **-0.78 [-0.90, -0.67]** |
| Heterogeneity: Tau² = 0.07; Chi² = 97.00, df = 40 (P < 0.00001); I² = 59% | | | | | | | | |
| Test for overall effect: Z = 13.53 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 1.43, df = 1 (P = 0.23), I² = 30.1% | | | | | | | | |



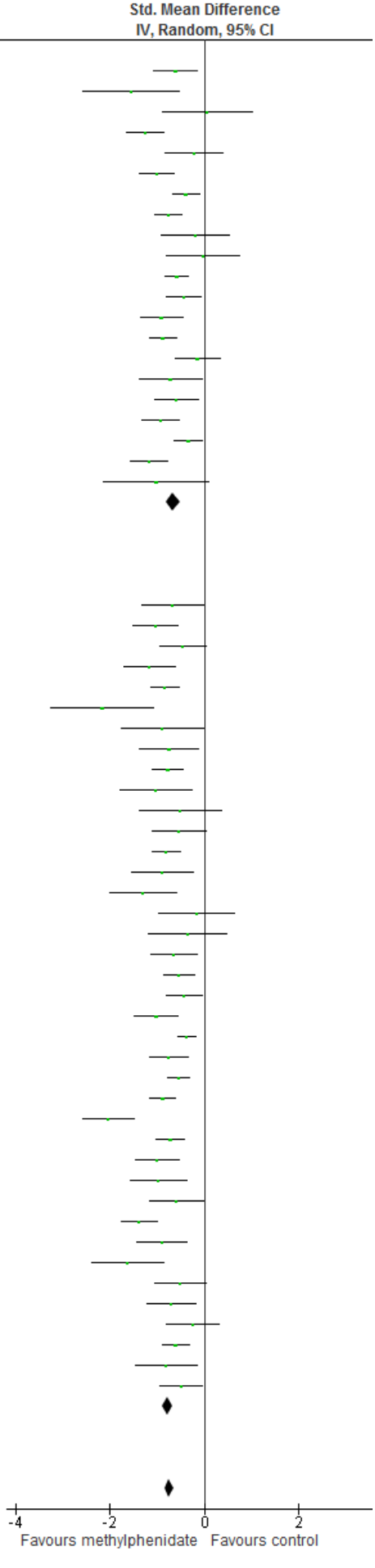
**3.9 ADHD symptoms, cross-over trials (endpoint data), subgroup analysis: dose**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **3.9.1 Low dose** | | | | | | | | |
| Barkley 2000 | 16.8 | 9.7 | 31 | 21.9 | 12.5 | 31 | 1.9% | -0.45 [-0.95, 0.05] |
| Brams 2008 | -16.382 | 14.0495 | 86 | -4.622 | 14.0495 | 86 | 2.6% | -0.83 [-1.15, -0.52] |
| Brown 1984a | 11 | 3.49 | 11 | 19.55 | 4.08 | 11 | 0.7% | -2.17 [-3.26, -1.07] |
| Brown 1988 | 31.5 | 5.85 | 11 | 39.66 | 3.61 | 11 | 0.8% | -1.61 [-2.60, -0.63] |
| Chronis 2003 | 2.6 | 2 | 21 | 3.1 | 1.9 | 21 | 1.5% | -0.25 [-0.86, 0.36] |
| Coghill 2007 | 67.2 | 13.5 | 75 | 77.2 | 11.1 | 75 | 2.5% | -0.81 [-1.14, -0.47] |
| Cook 1993 | 0.41 | 0.175 | 15 | 0.59 | 0.166 | 15 | 1.2% | -1.03 [-1.79, -0.26] |
| DuPaul 1996 | 19.42 | 9.58 | 24 | 21 | 9.28 | 24 | 1.7% | -0.16 [-0.73, 0.40] |
| Findling 2007 | 20.81 | 9.79 | 20 | 32.19 | 14.61 | 20 | 1.4% | -0.90 [-1.55, -0.24] |
| Fitzpatrick 1992a | 0.96 | 0.5 | 19 | 1.75 | 0.67 | 19 | 1.3% | -1.31 [-2.02, -0.60] |
| Flapper 2008 | 15.75 | 10.391 | 12 | 14.857 | 10.669 | 12 | 1.1% | 0.08 [-0.72, 0.88] |
| Gadow 1990 | 9.8 | 4.51 | 11 | 11 | 8.24 | 11 | 1.0% | -0.17 [-1.01, 0.66] |
| Gadow 1995 | 10.2 | 5.4 | 34 | 11.8 | 7.3 | 34 | 2.0% | -0.25 [-0.72, 0.23] |
| Gadow 2007 | 10 | 5.5 | 71 | 11 | 7 | 71 | 2.5% | -0.16 [-0.49, 0.17] |
| Gadow 2011 | 8.6 | 5.2 | 54 | 11.5 | 7.7 | 54 | 2.3% | -0.44 [-0.82, -0.06] |
| Hoeppner 1997 | 7.13 | 6.37 | 50 | 12.16 | 6.78 | 50 | 2.2% | -0.76 [-1.17, -0.35] |
| Kollins 2006 (PATS) | 1.28 | 0.73 | 165 | 1.47 | 0.7 | 165 | 3.0% | -0.27 [-0.48, -0.05] |
| Manos 1999 | 10.1 | 6.71 | 117 | 18.61 | 11.86 | 117 | 2.8% | -0.88 [-1.15, -0.61] |
| McBride 1988a | 6.5 | 3.9 | 41 | 17.4 | 6.4 | 41 | 1.8% | -2.04 [-2.58, -1.50] |
| McGough 2006 | 20.2 | 20.3481 | 93 | 35.3 | 21.3125 | 93 | 2.7% | -0.72 [-1.02, -0.42] |
| Musten 1997 | 67.03 | 15.39 | 41 | 77.23 | 14.1 | 41 | 2.1% | -0.68 [-1.13, -0.24] |
| Pearson 2013 | 61.9 | 11.7 | 24 | 66.8 | 12.7 | 24 | 1.6% | -0.39 [-0.97, 0.18] |
| Pelham 1999 | 1.7 | 1.5 | 25 | 3 | 2.7 | 25 | 1.7% | -0.59 [-1.15, -0.02] |
| Pelham 2005 | 2.7 | 2.2 | 30 | 5.5 | 3.8 | 30 | 1.8% | -0.89 [-1.42, -0.36] |
| Solanto 2009 | 61.64 | 10.39 | 30 | 65.8 | 13.98 | 30 | 1.8% | -0.33 [-0.84, 0.18] |
| Stein 1996 | 5.5 | 3.1 | 25 | 6.3 | 3.5 | 25 | 1.7% | -0.24 [-0.79, 0.32] |
| **Subtotal (95% CI)** | | | **1136** | | | **1136** | **47.6%** | **-0.65 [-0.82, -0.48]** |
| Heterogeneity: Tau² = 0.12; Chi² = 85.16, df = 25 (P < 0.00001); I² = 71% | | | | | | | | |
| Test for overall effect: Z = 7.55 (P < 0.00001) | | | | | | | | |
| **3.9.2 High dose** | | | | | | | | |
| Abikoff 2009 | 0.99 | 0.55 | 19 | 1.4 | 0.63 | 19 | 1.4% | -0.68 [-1.33, -0.02] |
| Barkley 1991 | 14.53 | 8.2 | 40 | 24.88 | 11.26 | 40 | 2.0% | -1.04 [-1.51, -0.57] |
| Blum 2011 | 64.8 | 26.5 | 30 | 89.6 | 13.1 | 30 | 1.7% | -1.17 [-1.72, -0.62] |
| Chronis 2003 | 1.8 | 1.5 | 21 | 3.1 | 1.9 | 21 | 1.5% | -0.75 [-1.37, -0.12] |
| Coghill 2007 | 67 | 14.8 | 75 | 77.2 | 11.1 | 75 | 2.5% | -0.78 [-1.11, -0.44] |
| Corkum 2008 | 62.14 | 14.11 | 10 | 69.38 | 10.23 | 11 | 1.0% | -0.57 [-1.45, 0.31] |
| DuPaul 1996 | 15.75 | 9.76 | 24 | 21 | 9.28 | 24 | 1.6% | -0.54 [-1.12, 0.03] |
| Epstein 2011 | 19.6 | 10.09 | 93 | 28.26 | 11.12 | 93 | 2.7% | -0.81 [-1.11, -0.51] |
| Flapper 2008 | 13 | 11.707 | 12 | 14.857 | 10.669 | 12 | 1.1% | -0.16 [-0.96, 0.64] |
| Gadow 1990 | 8.3 | 6.19 | 11 | 11 | 8.24 | 11 | 1.0% | -0.36 [-1.20, 0.49] |
| Gadow 1995 | 7.8 | 4.6 | 34 | 11.8 | 7.3 | 34 | 1.9% | -0.65 [-1.14, -0.16] |
| Gadow 2007 | 7.8 | 4.7 | 71 | 11 | 7 | 71 | 2.5% | -0.53 [-0.87, -0.20] |
| Gadow 2011 | 8.6 | 5.6 | 54 | 11.5 | 7.7 | 54 | 2.3% | -0.43 [-0.81, -0.05] |
| Gorman 2006 | 0.72 | 0.8324 | 41 | 1.61 | 0.8964 | 41 | 2.0% | -1.02 [-1.48, -0.56] |
| Grizenko 2012 | 56.76 | 11.87 | 198 | 61.64 | 14.19 | 198 | 3.0% | -0.37 [-0.57, -0.17] |
| Kollins 2006 (PATS) | 1.09 | 0.69 | 142 | 1.47 | 0.7 | 165 | 2.9% | -0.55 [-0.77, -0.32] |
| Musten 1997 | 63.29 | 13.44 | 41 | 77.23 | 14.1 | 41 | 2.0% | -1.00 [-1.46, -0.54] |
| Pearson 2013 | 55.8 | 9.3 | 24 | 66.8 | 12.7 | 24 | 1.6% | -0.97 [-1.57, -0.37] |
| Pelham 2001a | 11.41 | 6.23 | 68 | 19.91 | 6.02 | 68 | 2.3% | -1.38 [-1.75, -1.00] |
| Pelham 2005 | 2.3 | 2.2 | 30 | 5.5 | 3.8 | 30 | 1.7% | -1.02 [-1.56, -0.48] |
| Schachar 2008 | -0.98 | 2.14 | 18 | 3.2 | 2.82 | 18 | 1.2% | -1.63 [-2.40, -0.87] |
| Smithee 1998 | 0.8639 | 0.4415 | 26 | 1.141 | 0.61022 | 26 | 1.7% | -0.51 [-1.07, 0.04] |
| Solanto 2009 | 56.96 | 12.41 | 30 | 65.8 | 13.98 | 30 | 1.8% | -0.66 [-1.18, -0.14] |
| Stein 2011 | 20.27 | 13.557 | 93 | 29.12 | 15.077 | 101 | 2.7% | -0.61 [-0.90, -0.33] |
| Taylor 1987 | 0.38 | 0.46 | 37 | 0.81 | 0.76 | 37 | 2.0% | -0.68 [-1.15, -0.21] |
| Tirosh 1993a | 10.75 | 2.9 | 20 | 14 | 4.8 | 20 | 1.4% | -0.80 [-1.45, -0.16] |
| Zeiner 1999 | 3.08 | 3.7 | 38 | 5.25 | 5.01 | 38 | 2.0% | -0.49 [-0.94, -0.03] |
| Zeni 2009 | 1.6267 | 0.6894 | 6 | 1.2625 | 0.77765 | 8 | 0.7% | 0.46 [-0.62, 1.54] |
| **Subtotal (95% CI)** | | | **1306** | | | **1340** | **52.4%** | **-0.72 [-0.84, -0.60]** |
| Heterogeneity: Tau² = 0.05; Chi² = 53.22, df = 27 (P = 0.002); I² = 49% | | | | | | | | |
| Test for overall effect: Z = 11.65 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **2442** | | | **2476** | **100.0%** | **-0.69 [-0.79, -0.58]** |
| Heterogeneity: Tau² = 0.08; Chi² = 139.72, df = 53 (P < 0.00001); I² = 62% | | | | | | | | |
| Test for overall effect: Z = 13.22 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.41, df = 1 (P = 0.52), I² = 0% | | | | | | | | |



**3.10 Subgroup analysis: all parallel-group trials and first-period cross-over trials compared with cross-over trials (endpoint data)**

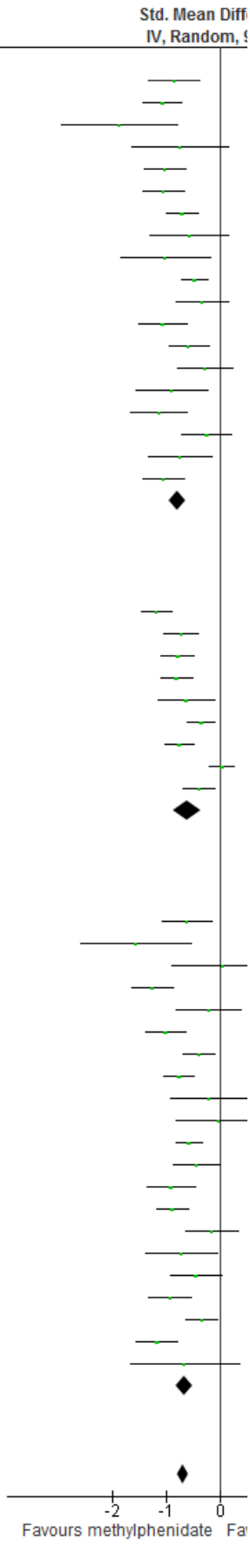
| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **3.10.1 All parallel-group trials and first-period cross-over trials** | | | | | | | | |
| Arnold 2004 | 0.8 | 0.7 | 35 | 1.3 | 0.9 | 40 | 1.8% | -0.61 [-1.07, -0.14] |
| Brown 1985 | 7.5 | 2.6 | 10 | 13.1 | 4.1 | 10 | 0.6% | -1.56 [-2.59, -0.53] |
| Carlson 2007 | -3.3 | 20.9 | 9 | -4.3 | 5.2 | 8 | 0.7% | 0.06 [-0.89, 1.01] |
| Childress 2009 | 19.6 | 12.75 | 57 | 35.9 | 13.01 | 63 | 2.0% | -1.26 [-1.65, -0.86] |
| Duric 2012 | 23.7 | 15.153 | 22 | 26.7 | 13.02 | 19 | 1.3% | -0.21 [-0.82, 0.41] |
| Findling 2006 | 5.1 | 2.9321 | 120 | 8.1 | 3.0232 | 39 | 2.1% | -1.01 [-1.39, -0.63] |
| Findling 2008 | 28.4 | 21.07 | 94 | 37 | 23.39 | 88 | 2.5% | -0.39 [-0.68, -0.09] |
| Findling 2010 | 36.52 | 17.6537 | 143 | 50 | 17.6537 | 72 | 2.5% | -0.76 [-1.05, -0.47] |
| Firestone 1981 | 13.5 | 7.26 | 18 | 14.9 | 6.58 | 13 | 1.1% | -0.20 [-0.91, 0.52] |
| Ialongo 1994 | 9.76 | 5.94 | 13 | 9.9 | 4.28 | 12 | 0.9% | -0.03 [-0.81, 0.76] |
| Jensen 1999 (MTA) | 0.85 | 0.63 | 133 | 1.24 | 0.72 | 129 | 2.7% | -0.58 [-0.82, -0.33] |
| Kollins 2006 (PATS) | 1.09 | 0.72 | 61 | 1.41 | 0.77 | 53 | 2.1% | -0.43 [-0.80, -0.06] |
| Lehmkuhl 2002 | 1.1 | 0.6557 | 43 | 1.7 | 0.6481 | 42 | 1.8% | -0.91 [-1.36, -0.46] |
| Newcorn 2008 | -10.2 | 9.1 | 195 | -2.3 | 8.4 | 66 | 2.5% | -0.88 [-1.17, -0.59] |
| Schachar 1997a | 1.2 | 0.7 | 37 | 1.3 | 0.7 | 29 | 1.7% | -0.14 [-0.63, 0.35] |
| Szobot 2004 | 11.9 | 6.1 | 19 | 16.4 | 6.2 | 17 | 1.1% | -0.72 [-1.39, -0.04] |
| Taylor 1987 | 0.36 | 0.42 | 39 | 0.68 | 0.64 | 39 | 1.8% | -0.59 [-1.04, -0.13] |
| Tucker 2009 | -8.2 | 6.05 | 53 | -3.2 | 4.6 | 56 | 2.0% | -0.93 [-1.32, -0.53] |
| Wilens 2006b | 16.65 | 11.07 | 87 | 20.84 | 13.58 | 90 | 2.4% | -0.34 [-0.63, -0.04] |
| Wolraich 2001 | 5.44 | 3.22 | 81 | 9.48 | 3.78 | 46 | 2.0% | -1.17 [-1.56, -0.78] |
| Zeni 2009 | 1.2022 | 0.65764 | 9 | 1.9317 | 0.69847 | 6 | 0.5% | -1.02 [-2.14, 0.10] |
| **Subtotal (95% CI)** | | | **1278** | | | **937** | **36.1%** | **-0.66 [-0.82, -0.51]** |
| Heterogeneity: Tau² = 0.07; Chi² = 50.55, df = 20 (P = 0.0002); I² = 60% | | | | | | | | |
| Test for overall effect: Z = 8.52 (P < 0.00001) | | | | | | | | |
| **3.10.2 Cross-over trials (endpoint data)** | | | | | | | | |
| Abikoff 2009 | 0.99 | 0.55 | 19 | 1.4 | 0.63 | 19 | 1.2% | -0.68 [-1.33, -0.02] |
| Barkley 1991 | 14.53 | 8.2 | 40 | 24.88 | 11.26 | 40 | 1.7% | -1.04 [-1.51, -0.57] |
| Barkley 2000 | 16.8 | 9.7 | 31 | 21.9 | 12.5 | 31 | 1.6% | -0.45 [-0.95, 0.05] |
| Blum 2011 | 64.8 | 26.5 | 30 | 89.6 | 13.1 | 30 | 1.5% | -1.17 [-1.72, -0.62] |
| Brams 2008 | -16.382 | 14.0495 | 86 | -4.622 | 14.0495 | 86 | 2.4% | -0.83 [-1.15, -0.52] |
| Brown 1984a | 11 | 3.49 | 11 | 19.55 | 4.08 | 11 | 0.6% | -2.17 [-3.26, -1.07] |
| Brown 1988 | 36.5 | 3.2 | 11 | 39.66 | 3.61 | 11 | 0.8% | -0.89 [-1.78, -0.01] |
| Chronis 2003 | 1.8 | 1.5 | 21 | 3.1 | 1.9 | 21 | 1.3% | -0.75 [-1.37, -0.12] |
| Coghill 2007 | 67 | 14.8 | 75 | 77.2 | 11.1 | 75 | 2.3% | -0.78 [-1.11, -0.44] |
| Cook 1993 | 0.41 | 0.175 | 15 | 0.59 | 0.166 | 15 | 1.0% | -1.03 [-1.79, -0.26] |
| Corkum 2008 | 63.05 | 13.89 | 10 | 69.38 | 10.23 | 11 | 0.8% | -0.50 [-1.37, 0.37] |
| DuPaul 1996 | 15.75 | 9.76 | 24 | 21 | 9.28 | 24 | 1.4% | -0.54 [-1.12, 0.03] |
| Epstein 2011 | 19.6 | 10.09 | 93 | 28.26 | 11.12 | 93 | 2.4% | -0.81 [-1.11, -0.51] |
| Findling 2007 | 20.81 | 9.79 | 20 | 32.19 | 14.61 | 20 | 1.2% | -0.90 [-1.55, -0.24] |
| Fitzpatrick 1992a | 0.96 | 0.5 | 19 | 1.75 | 0.67 | 19 | 1.1% | -1.31 [-2.02, -0.60] |
| Flapper 2008 | 13 | 11.707 | 12 | 14.857 | 10.669 | 12 | 0.9% | -0.16 [-0.96, 0.64] |
| Gadow 1990 | 8.3 | 6.1 | 11 | 11 | 8.24 | 11 | 0.8% | -0.36 [-1.20, 0.49] |
| Gadow 1995 | 7.8 | 4.6 | 34 | 11.8 | 7.3 | 34 | 1.7% | -0.65 [-1.14, -0.16] |
| Gadow 2007 | 7.8 | 4.7 | 71 | 11 | 7 | 71 | 2.3% | -0.53 [-0.87, -0.20] |
| Gadow 2011 | 8.6 | 5.6 | 54 | 11.5 | 7.7 | 54 | 2.1% | -0.43 [-0.81, -0.05] |
| Gorman 2006 | 0.72 | 0.8324 | 41 | 1.61 | 0.8964 | 41 | 1.8% | -1.02 [-1.48, -0.56] |
| Grizenko 2012 | 56.76 | 11.87 | 198 | 61.64 | 14.19 | 198 | 2.9% | -0.37 [-0.57, -0.17] |
| Hoeppner 1997 | 7.13 | 6.37 | 50 | 12.16 | 6.78 | 50 | 2.0% | -0.76 [-1.17, -0.35] |
| Kollins 2006 (PATS) | 1.09 | 0.69 | 142 | 1.47 | 0.7 | 165 | 2.7% | -0.55 [-0.77, -0.32] |
| Manos 1999 | 10.1 | 6.71 | 117 | 18.61 | 11.86 | 117 | 2.6% | -0.88 [-1.15, -0.61] |
| McBride 1988a | 6.5 | 3.9 | 41 | 17.4 | 6.4 | 41 | 1.5% | -2.04 [-2.58, -1.50] |
| McGough 2006 | 20.2 | 20.3481 | 93 | 35.3 | 21.3125 | 93 | 2.4% | -0.72 [-1.02, -0.42] |
| Musten 1997 | 63.29 | 13.44 | 41 | 77.23 | 14.1 | 41 | 1.8% | -1.00 [-1.46, -0.54] |
| Pearson 2013 | 55.8 | 9.3 | 24 | 66.8 | 12.7 | 24 | 1.3% | -0.97 [-1.57, -0.37] |
| Pelham 1999 | 1.7 | 1.5 | 25 | 3 | 2.7 | 25 | 1.4% | -0.59 [-1.15, -0.02] |
| Pelham 2001a | 11.41 | 6.23 | 68 | 19.91 | 6.02 | 68 | 2.1% | -1.38 [-1.75, -1.00] |
| Pelham 2005 | 2.7 | 2.2 | 30 | 5.5 | 3.8 | 30 | 1.5% | -0.89 [-1.42, -0.36] |
| Schachar 2008 | -0.98 | 2.14 | 18 | 3.2 | 2.82 | 18 | 1.0% | -1.63 [-2.40, -0.87] |
| Smithee 1998 | 0.8639 | 0.4415 | 26 | 1.141 | 0.61022 | 26 | 1.5% | -0.51 [-1.07, 0.04] |
| Solanto 2009 | 56.96 | 10.57 | 30 | 65.8 | 13.98 | 30 | 1.6% | -0.70 [-1.23, -0.18] |
| Stein 1996 | 5.5 | 3.1 | 25 | 6.3 | 3.5 | 25 | 1.5% | -0.24 [-0.79, 0.32] |
| Stein 2011 | 20.27 | 13.557 | 93 | 29.12 | 15.077 | 101 | 2.5% | -0.61 [-0.90, -0.33] |
| Tirosh 1993a | 10.75 | 2.9 | 20 | 14 | 4.8 | 20 | 1.2% | -0.80 [-1.45, -0.16] |
| Zeiner 1999 | 3.08 | 3.7 | 38 | 5.25 | 5.01 | 38 | 1.8% | -0.49 [-0.94, -0.03] |
| **Subtotal (95% CI)** | | | **1807** | | | **1839** | **63.9%** | **-0.79 [-0.90, -0.67]** |
| Heterogeneity: Tau² = 0.06; Chi² = 88.64, df = 38 (P < 0.00001); I² = 57% | | | | | | | | |
| Test for overall effect: Z = 13.71 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **3085** | | | **2776** | **100.0%** | **-0.74 [-0.83, -0.65]** |
| Heterogeneity: Tau² = 0.06; Chi² = 140.36, df = 59 (P < 0.00001); I² = 58% | | | | | | | | |
| Test for overall effect: Z = 16.20 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 1.61, df = 1 (P = 0.20), I² = 38.0% | | | | | | | | |



## 4 - Additional subgroup analyses of ADHD symptoms: parallel-group trials and first-period cross-over trials

### 4.1 Comparision of raters

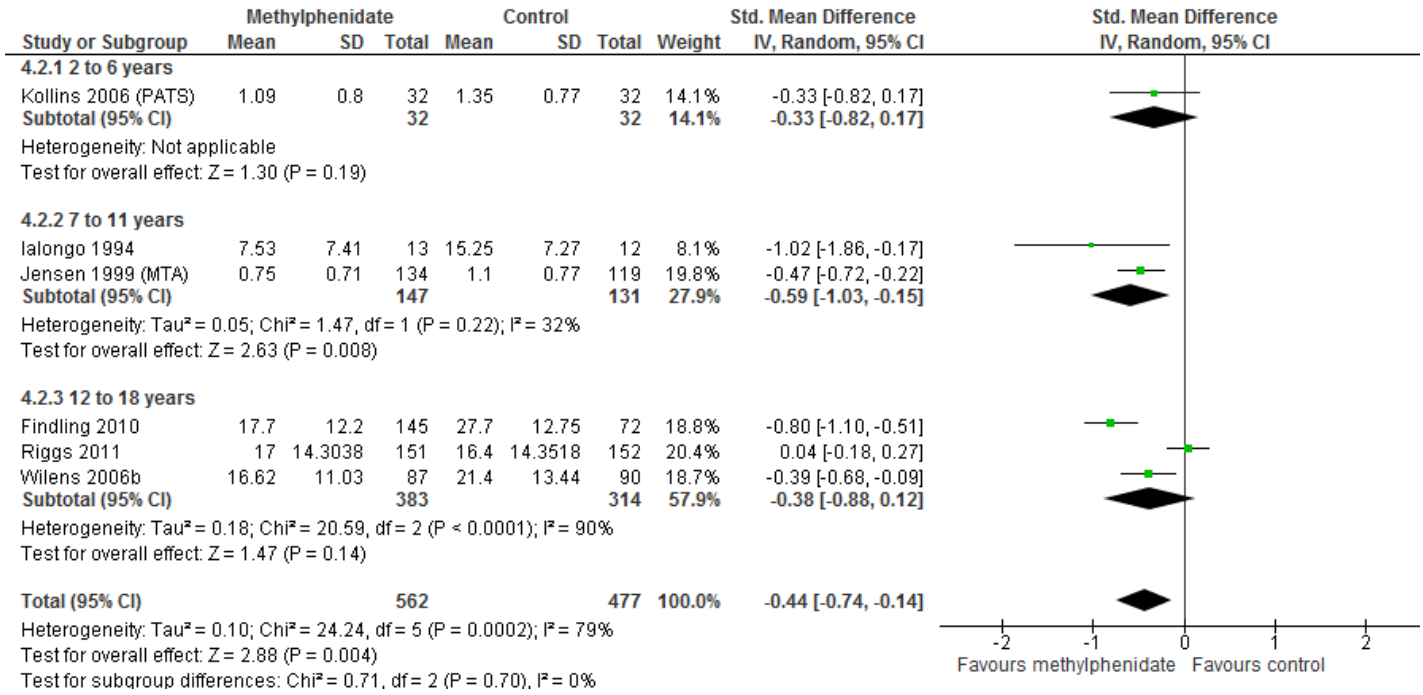
| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **4.1.1 Teacher-rated** | | | | | | | | |
| Arnold 2004 | 0.7 | 0.7 | 35 | 1.4 | 0.9 | 40 | 2.0% | -0.85 [-1.33, -0.38] |
| Biederman 2003 | 16.3 | 12.12 | 63 | 31.3 | 15.37 | 71 | 2.4% | -1.07 [-1.43, -0.71] |
| Brown 1985 (1) | 15 | 3.1 | 10 | 20.6 | 2.6 | 10 | 0.7% | -1.87 [-2.96, -0.78] |
| Butter 1983 | 30.47 | 17.3 | 10 | 42.7 | 14.2 | 10 | 0.9% | -0.74 [-1.65, 0.17] |
| Childress 2009 | 16.4 | 13.44 | 57 | 30 | 13.01 | 63 | 2.3% | -1.02 [-1.40, -0.64] |
| Findling 2006 | 4.3 | 3.264 | 120 | 7.7 | 3.1157 | 39 | 2.3% | -1.05 [-1.43, -0.67] |
| Findling 2008 | 18.3 | 17.44 | 94 | 31.6 | 20.07 | 88 | 2.6% | -0.71 [-1.01, -0.41] |
| Firestone 1981 | 8.9 | 4.93 | 18 | 11.77 | 4.83 | 13 | 1.3% | -0.57 [-1.30, 0.16] |
| Ialongo 1994 | 7.53 | 7.41 | 13 | 15.25 | 7.27 | 12 | 1.0% | -1.02 [-1.86, -0.17] |
| Jensen 1999 (MTA) | 0.75 | 0.71 | 134 | 1.1 | 0.77 | 119 | 2.8% | -0.47 [-0.72, -0.22] |
| Kollins 2006 (PATS) | 1.09 | 0.8 | 32 | 1.35 | 0.77 | 32 | 1.9% | -0.33 [-0.82, 0.17] |
| Lehmkuhl 2002 | 0.9 | 0.6557 | 43 | 1.6 | 0.6481 | 42 | 2.1% | -1.06 [-1.52, -0.61] |
| Moshe 2012 | 58 | 10.3 | 57 | 64.7 | 12.5 | 57 | 2.4% | -0.58 [-0.96, -0.21] |
| Palumbo 2008 | -5.07 | 6.79 | 29 | -3.2 | 6.38 | 30 | 1.9% | -0.28 [-0.79, 0.23] |
| Pliszka 2000 | 0.81 | 0.62 | 20 | 1.49 | 0.87 | 18 | 1.4% | -0.89 [-1.56, -0.22] |
| Schachar 1997a | 0.9 | 0.7 | 37 | 1.7 | 0.7 | 29 | 1.8% | -1.13 [-1.65, -0.60] |
| Tourette's Syndrome Study Group 2002 | 1.315 | 6.13 | 37 | 2.82 | 6.13 | 32 | 2.0% | -0.24 [-0.72, 0.23] |
| Van der Meere 1999a | 73.6 | 12.7133 | 24 | 83.1 | 12.7133 | 24 | 1.6% | -0.73 [-1.32, -0.15] |
| Wolraich 2001 | 5.7 | 3.84 | 81 | 9.87 | 4.09 | 46 | 2.3% | -1.05 [-1.44, -0.67] |
| **Subtotal (95% CI)** | | | **914** | | | **775** | **35.8%** | **-0.78 [-0.93, -0.63]** |
| Heterogeneity: Tau² = 0.05; Chi² = 34.54, df = 18 (P = 0.01); I² = 48% | | | | | | | | |
| Test for overall effect: Z = 10.30 (P < 0.00001) | | | | | | | | |
| **4.1.2 Independent assessor-rated** | | | | | | | | |
| Coghill 2013 | 3.5295 | 10.9979 | 111 | 16.5295 | 10.9979 | 110 | 2.7% | -1.18 [-1.46, -0.89] |
| Döpfner 2004 | 0.441 | 0.427 | 82 | 0.858 | 0.689 | 82 | 2.6% | -0.72 [-1.04, -0.41] |
| Findling 2008 | -21.619 | 14.409 | 91 | -10.3 | 14.409 | 85 | 2.6% | -0.78 [-1.09, -0.48] |
| Findling 2010 | 17.7 | 12.2 | 145 | 27.7 | 12.75 | 72 | 2.7% | -0.80 [-1.10, -0.51] |
| Gonzalez-Heydrich 2010 | 23 | 12 | 28 | 30 | 10 | 28 | 1.8% | -0.62 [-1.16, -0.09] |
| Jensen 1999 (MTA) | 0.21 | 0.2 | 114 | 0.29 | 0.26 | 107 | 2.8% | -0.35 [-0.61, -0.08] |
| Newcorn 2008 | -16.9 | 13.1 | 220 | -7.3 | 11.5 | 74 | 2.8% | -0.75 [-1.02, -0.48] |
| Riggs 2011 | 17 | 14.3038 | 151 | 16.4 | 14.3518 | 152 | 2.9% | 0.04 [-0.18, 0.27] |
| Wilens 2006b | 16.62 | 11.03 | 87 | 21.4 | 13.44 | 90 | 2.7% | -0.39 [-0.68, -0.09] |
| **Subtotal (95% CI)** | | | **1029** | | | **800** | **23.5%** | **-0.61 [-0.87, -0.35]** |
| Heterogeneity: Tau² = 0.14; Chi² = 56.91, df = 8 (P < 0.00001); I² = 86% | | | | | | | | |
| Test for overall effect: Z = 4.57 (P < 0.00001) | | | | | | | | |
| **4.1.3 Parent-rated** | | | | | | | | |
| Arnold 2004 | 0.8 | 0.7 | 35 | 1.3 | 0.9 | 40 | 2.0% | -0.61 [-1.07, -0.14] |
| Brown 1985 | 7.5 | 2.6 | 10 | 13.1 | 4.1 | 10 | 0.8% | -1.56 [-2.59, -0.53] |
| Carlson 2007 | -3.3 | 20.9 | 9 | -4.3 | 5.2 | 8 | 0.9% | 0.06 [-0.89, 1.01] |
| Childress 2009 | 19.6 | 12.75 | 57 | 35.9 | 13.01 | 63 | 2.3% | -1.26 [-1.65, -0.86] |
| Duric 2012 | 23.7 | 15.153 | 22 | 26.7 | 13.02 | 19 | 1.5% | -0.21 [-0.82, 0.41] |
| Findling 2006 | 5.1 | 2.9321 | 120 | 8.1 | 3.0232 | 39 | 2.3% | -1.01 [-1.39, -0.63] |
| Findling 2008 | 28.4 | 21.07 | 94 | 37 | 23.39 | 88 | 2.7% | -0.39 [-0.68, -0.09] |
| Findling 2010 | 36.52 | 17.6537 | 143 | 50 | 17.6537 | 72 | 2.7% | -0.76 [-1.05, -0.47] |
| Firestone 1981 | 13.5 | 7.26 | 18 | 14.9 | 6.58 | 13 | 1.3% | -0.20 [-0.91, 0.52] |
| Ialongo 1994 | 9.76 | 5.94 | 13 | 9.9 | 4.28 | 12 | 1.2% | -0.03 [-0.81, 0.76] |
| Jensen 1999 (MTA) | 0.85 | 0.63 | 133 | 1.24 | 0.72 | 129 | 2.8% | -0.58 [-0.82, -0.33] |
| Kollins 2006 (PATS) | 1.09 | 0.72 | 48 | 1.41 | 0.77 | 38 | 2.1% | -0.43 [-0.86, 0.00] |
| Lehmkuhl 2002 | 1.1 | 0.6557 | 43 | 1.7 | 0.6481 | 42 | 2.1% | -0.91 [-1.36, -0.46] |
| Newcorn 2008 | -10.2 | 9.1 | 195 | -2.3 | 8.4 | 66 | 2.7% | -0.88 [-1.17, -0.59] |
| Schachar 1997a | 1.2 | 0.7 | 37 | 1.3 | 0.7 | 29 | 1.9% | -0.14 [-0.63, 0.35] |
| Szobot 2004 | 11.9 | 6.1 | 19 | 16.4 | 6.2 | 17 | 1.4% | -0.72 [-1.39, -0.04] |
| Tourette's Syndrome Study Group 2002 | 2.85 | 7.08 | 37 | 6 | 7.01 | 32 | 2.0% | -0.44 [-0.92, 0.04] |
| Tucker 2009 | -8.2 | 6.05 | 53 | -3.2 | 4.6 | 56 | 2.3% | -0.93 [-1.32, -0.53] |
| Wilens 2006b | 16.65 | 11.07 | 87 | 20.84 | 13.58 | 90 | 2.7% | -0.34 [-0.63, -0.04] |
| Wolraich 2001 | 5.44 | 3.22 | 81 | 9.48 | 3.78 | 46 | 2.3% | -1.17 [-1.56, -0.78] |
| Zeni 2009 | 1.2789 | 0.45518 | 9 | 1.7529 | 0.90373 | 7 | 0.8% | -0.65 [-1.68, 0.37] |
| **Subtotal (95% CI)** | | | **1263** | | | **916** | **40.7%** | **-0.65 [-0.81, -0.50]** |
| Heterogeneity: Tau² = 0.07; Chi² = 50.49, df = 20 (P = 0.0002); I² = 60% | | | | | | | | |
| Test for overall effect: Z = 8.31 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **3206** | | | **2491** | **100.0%** | **-0.69 [-0.79, -0.59]** |
| Heterogeneity: Tau² = 0.08; Chi² = 149.62, df = 48 (P < 0.00001); I² = 68% | | | | | | | | |
| Test for overall effect: Z = 13.01 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 2.00, df = 2 (P = 0.37), I² = 0.0% | | | | | | | | |



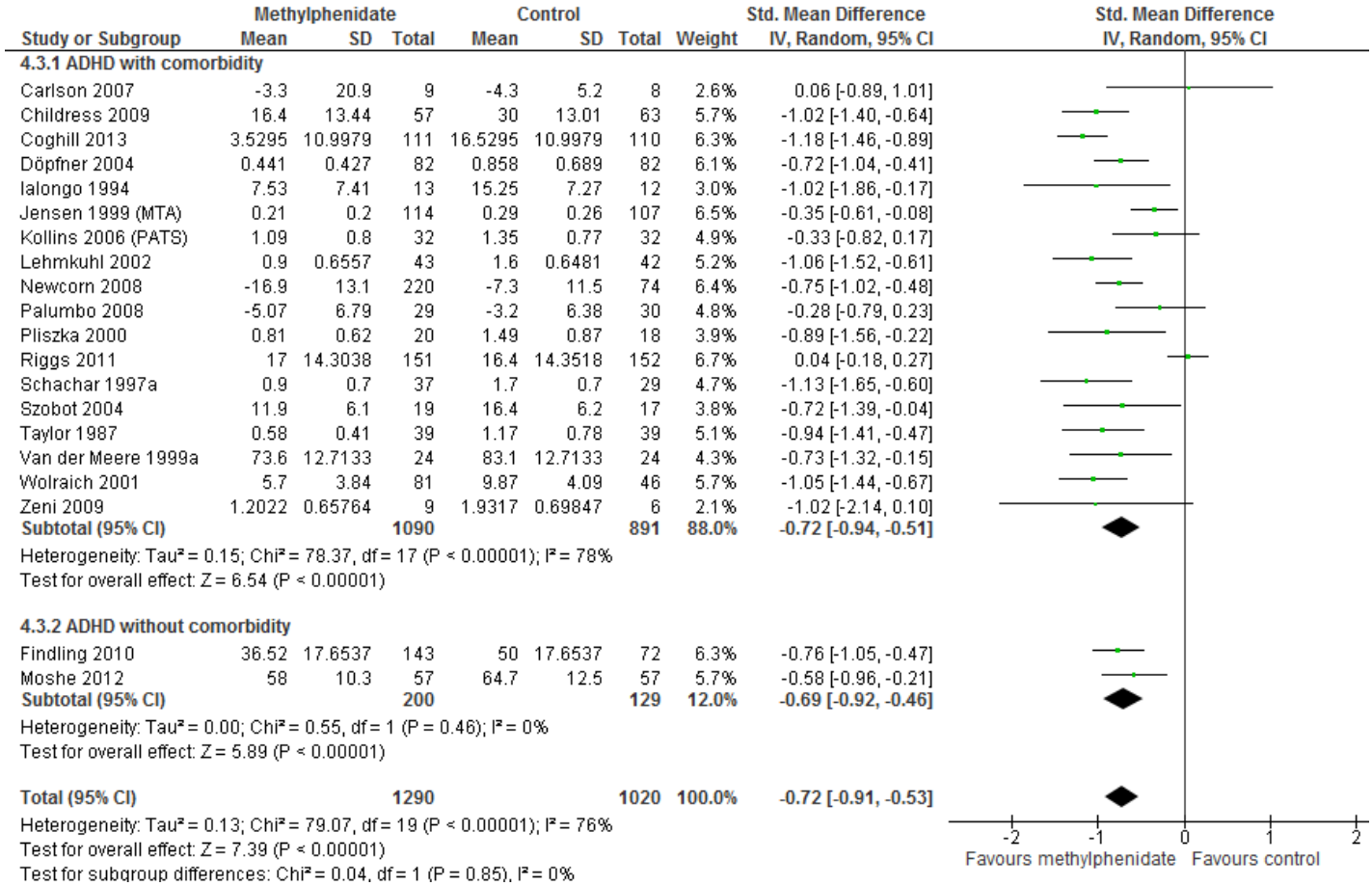

Footnotes

(1) MPH vs waiting list

4.2 Age

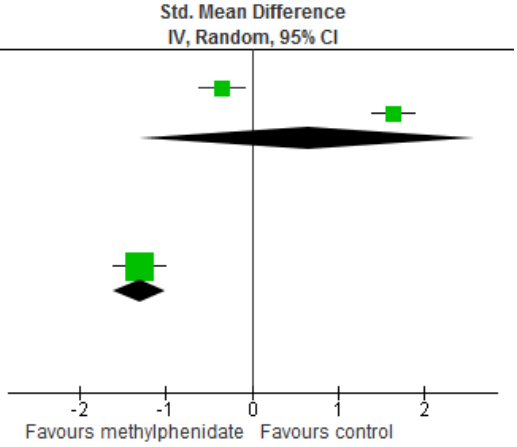



4.3 Comorbidity versus no comorbidity



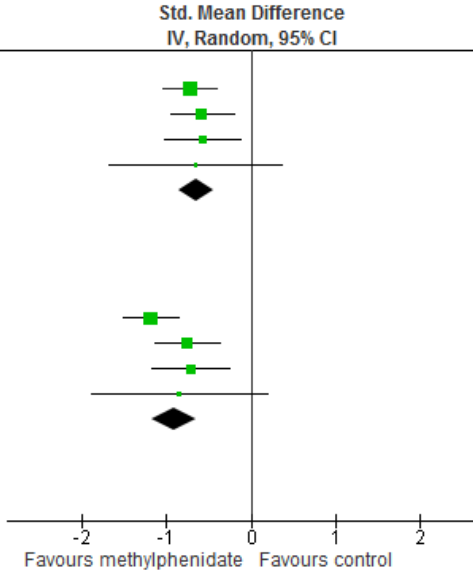
**4.4 Subtypes ADHD: ADHD Rating Scale (parent-, teacher- or independent assessor-rated)**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **4.4.1 Combined ADHD** | | | | | | | | |
| Jensen 1999 (MTA) | 0.21 | 0.2 | 114 | 0.29 | 0.26 | 107 | 50.0% | -0.35 [-0.61, -0.08] |
| Riggs 2011 | 18.9 | 1.3 | 169 | 16.5 | 1.6 | 169 | 50.0% | 1.64 [1.40, 1.89] |
| **Subtotal (95% CI)** | | | **283** | | | **276** | **100.0%** | **0.65 [-1.30, 2.60]** |
| Heterogeneity: Tau² = 1.96; Chi² = 115.32, df = 1 (P < 0.00001); I² = 99% | | | | | | | | |
| Test for overall effect: Z = 0.65 (P = 0.51) | | | | | | | | |
| **4.4.2 Inattentive ADHD** | | | | | | | | |
| Riggs 2011 | 16.8 | 1.7 | 102 | 19.1 | 1.8 | 102 | 100.0% | -1.31 [-1.61, -1.01] |
| **Subtotal (95% CI)** | | | **102** | | | **102** | **100.0%** | **-1.31 [-1.61, -1.01]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 8.47 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 3.79, df = 1 (P = 0.05), I² = 73.6% | | | | | | | | |




**4.5 Cross-over trials: first-period data versus endpoint data (parent-, independent assessor- and teacher-rated)**

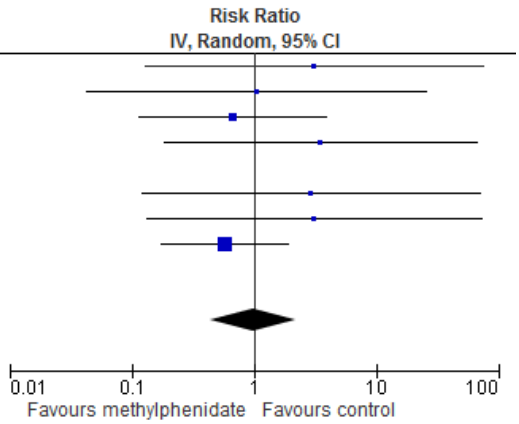
| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **4.5.1 First-period data** | | | | | | | | |
| Döpfner 2004 | 0.441 | 0.427 | 82 | 0.858 | 0.689 | 82 | 43.6% | -0.72 [-1.04, -0.41] |
| Moshe 2012 | 58 | 10.3 | 57 | 64.7 | 12.5 | 57 | 31.0% | -0.58 [-0.96, -0.21] |
| Taylor 1987 | 0.54 | 1.04 | 39 | 1.22 | 1.3 | 39 | 21.2% | -0.57 [-1.03, -0.12] |
| Zeni 2009 | 1.2789 | 0.45518 | 9 | 1.7529 | 0.90373 | 7 | 4.2% | -0.65 [-1.68, 0.37] |
| **Subtotal (95% CI)** | | | **187** | | | **185** | **100.0%** | **-0.64 [-0.85, -0.44]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.45, df = 3 (P = 0.93); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 6.05 (P < 0.00001) | | | | | | | | |
| **4.5.2 Endpoint data** | | | | | | | | |
| Döpfner 2004 | 0.374 | 0.366 | 82 | 1.081 | 0.751 | 82 | 37.7% | -1.19 [-1.52, -0.86] |
| Moshe 2012 | 55.5 | 9.5 | 57 | 62.1 | 7.9 | 57 | 31.8% | -0.75 [-1.13, -0.37] |
| Taylor 1987 | 0.85 | 1 | 39 | 1.59 | 1.04 | 39 | 24.5% | -0.72 [-1.18, -0.26] |
| Zeni 2009 | 0.8911 | 0.72428 | 9 | 1.7 | 1.0996 | 7 | 6.0% | -0.85 [-1.89, 0.20] |
| **Subtotal (95% CI)** | | | **187** | | | **185** | **100.0%** | **-0.91 [-1.18, -0.65]** |
| Heterogeneity: Tau² = 0.02; Chi² = 4.07, df = 3 (P = 0.25); I² = 26% | | | | | | | | |
| Test for overall effect: Z = 6.80 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 2.47, df = 1 (P = 0.12), I² = 59.6% | | | | | | | | |




## 5 - Number of serious adverse events: parallel-group trials and first-period cross-over trials

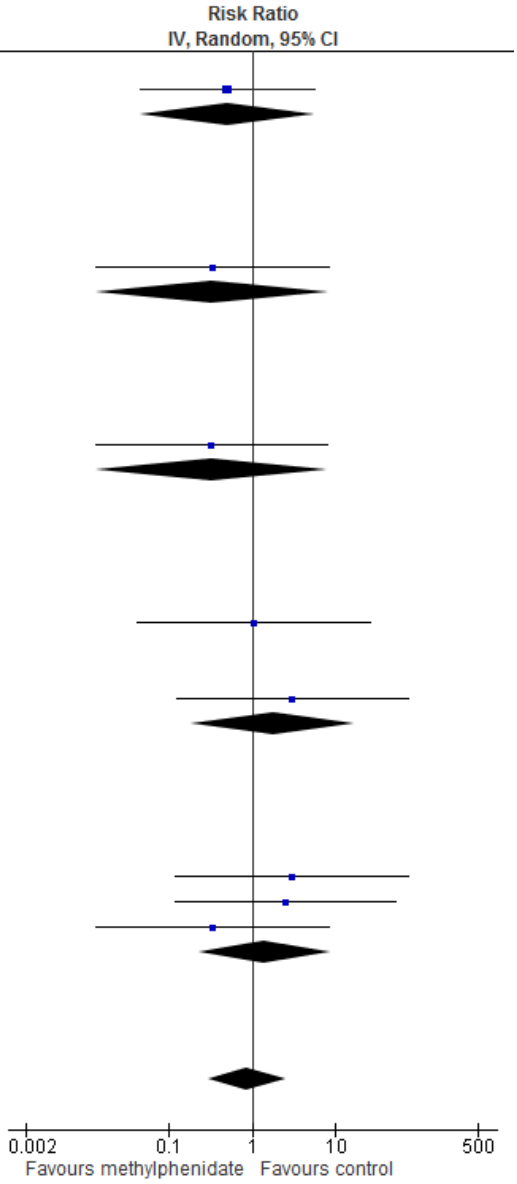
**5.1 Number of serious adverse events (SAE)**

| Study or Subgroup | Methylphenidate Events | Total | Control Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Carlson 2007 | 1 | 87 | 0 | 90 | 6.5% | 3.10 [0.13, 75.14] |
| Childress 2009 | 1 | 182 | 0 | 63 | 6.5% | 1.05 [0.04, 25.43] |
| Coghill 2013 | 2 | 110 | 3 | 111 | 21.1% | 0.67 [0.11, 3.95] |
| Findling 2010 | 3 | 145 | 0 | 72 | 7.6% | 3.50 [0.18, 66.86] |
| Jacobi-Polishook 2009 | 0 | 12 | 0 | 12 | | Not estimable |
| Lehmkuhl 2002 | 1 | 43 | 0 | 42 | 6.6% | 2.93 [0.12, 70.00] |
| Palumbo 2008 | 1 | 29 | 0 | 30 | 6.6% | 3.10 [0.13, 73.14] |
| Riggs 2011 | 4 | 151 | 7 | 152 | 45.2% | 0.58 [0.17, 1.92] |
| Wolraich 2001 | 0 | 160 | 0 | 41 | | Not estimable |
| **Total (95% CI)** | | **919** | | **613** | **100.0%** | **0.98 [0.44, 2.22]** |
| Total events | 13 | | 10 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 3.11, df = 6 (P = 0.80); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.04 (P = 0.97) | | | | | | |



5.2 Nervous system

| Study or Subgroup | Methylphenidate Events | Total | Control Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **5.2.1 Aggression** | | | | | | |
| Riggs 2011 | 1 | 151 | 2 | 152 | 20.0% | 0.50 [0.05, 5.49] |
| **Subtotal (95% CI)** | | **151** | | **152** | **20.0%** | **0.50 [0.05, 5.49]** |
| Total events | 1 | | 2 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.56 (P = 0.57) | | | | | | |
| **5.2.2 Concussion** | | | | | | |
| Riggs 2011 | 0 | 151 | 1 | 152 | 11.2% | 0.34 [0.01, 8.17] |
| **Subtotal (95% CI)** | | **151** | | **152** | **11.2%** | **0.34 [0.01, 8.17]** |
| Total events | 0 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.67 (P = 0.50) | | | | | | |
| **5.2.3 Loss of consciousness** | | | | | | |
| Coghill 2013 | 0 | 111 | 1 | 110 | 11.2% | 0.33 [0.01, 8.02] |
| **Subtotal (95% CI)** | | **111** | | **110** | **11.2%** | **0.33 [0.01, 8.02]** |
| Total events | 0 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.68 (P = 0.50) | | | | | | |
| **5.2.4 Psychosis** | | | | | | |
| Childress 2009 | 1 | 188 | 0 | 65 | 11.3% | 1.05 [0.04, 25.40] |
| Green 2011 | 0 | 22 | 0 | 12 | | Not estimable |
| Palumbo 2008 | 0 | 61 | 0 | 61 | | Not estimable |
| Riggs 2011 | 1 | 151 | 0 | 152 | 11.2% | 3.02 [0.12, 73.54] |
| **Subtotal (95% CI)** | | **422** | | **290** | **22.5%** | **1.78 [0.19, 16.96]** |
| Total events | 2 | | 0 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.50 (P = 0.62) | | | | | | |
| **5.2.5 Syncope** | | | | | | |
| Coghill 2013 | 1 | 111 | 0 | 110 | 11.2% | 2.97 [0.12, 72.20] |
| Findling 2010 (1) | 2 | 145 | 0 | 72 | 12.5% | 2.50 [0.12, 51.40] |
| Riggs 2011 | 0 | 151 | 1 | 152 | 11.2% | 0.34 [0.01, 8.17] |
| **Subtotal (95% CI)** | | **407** | | **334** | **35.0%** | **1.39 [0.23, 8.47]** |
| Total events | 3 | | 1 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 1.12, df = 2 (P = 0.57); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.36 (P = 0.72) | | | | | | |
| **Total (95% CI)** | | **1242** | | **1038** | **100.0%** | **0.87 [0.30, 2.53]** |
| Total events | 6 | | 5 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 2.87, df = 7 (P = 0.90); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.26 (P = 0.80) | | | | | | |
| Test for subgroup differences: Chi² = 1.54, df = 4 (P = 0.82), I² = 0% | | | | | | |

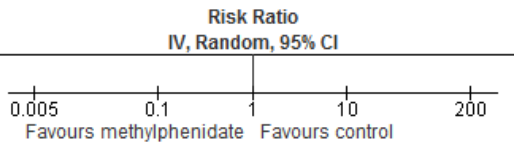



Footnotes

(1) samme patient = 2 events

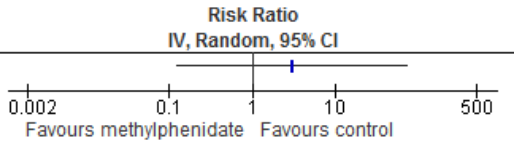
5.3 Digestive system: gastrointestinal disorders

| Study or Subgroup | Methylphenidate Events | Total | Control Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Coghill 2013 | 0 | 111 | 0 | 110 | | Not estimable |



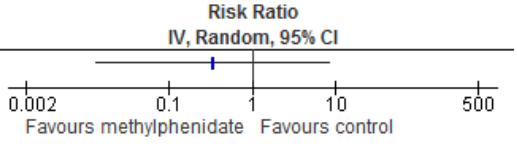

5.4 Urinary system: kidney infection

| Study or Subgroup | Methylphenidate Events | Total | Control Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Riggs 2011 | 1 | 151 | 0 | 152 | | 3.02 [0.12, 73.54] |



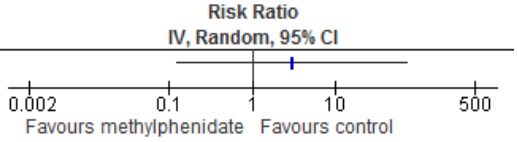

5.5 Circulatory and respiratory systems: asthma

| Study or Subgroup | Methylphenidate Events | Total | Control Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Riggs 2011 | 0 | 151 | 1 | 152 | | 0.34 [0.01, 8.17] |



**5.6 Immune system: cyst rupture**

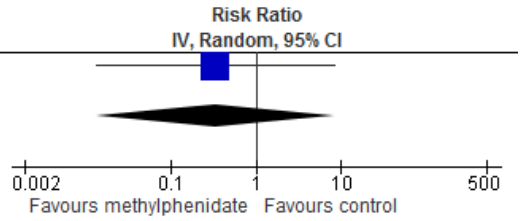
| Study or Subgroup | Methylphenidate Events | Total | Control Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Riggs 2011 | 1 | 151 | 0 | 152 | | 3.02 [0.12, 73.54] |




**5.7 Other: drug toxicity**

| Study or Subgroup | Methylphenidate Events | Total | Control Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Riggs 2011 | 0 | 151 | 1 | 152 | 100.0% | 0.34 [0.01, 8.17] |
| **Total (95% CI)** | | **151** | | **152** | **100.0%** | **0.34 [0.01, 8.17]** |
| Total events | 0 | | 1 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)

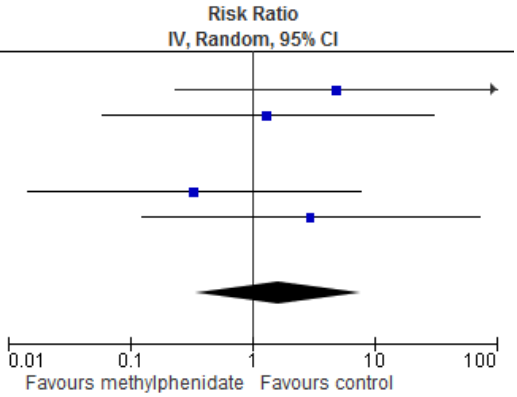



## 6 - Number of serious adverse events: cross-over trials (endpoint data)

**6.1 Number of serious adverse events (SAE)**

| Study or Subgroup | Methylphenidate Events | Total | Control Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Brams 2008 | 0 | 86 | 0 | 86 | | Not estimable |
| Brams 2012 | 2 | 163 | 0 | 159 | 26.5% | 4.88 [0.24, 100.82] |
| Buitelaar 1995 | 1 | 26 | 0 | 11 | 24.8% | 1.33 [0.06, 30.42] |
| Cox 2006 | 0 | 35 | 0 | 35 | | Not estimable |
| Grizenko 2012 | 0 | 430 | 0 | 430 | | Not estimable |
| Schachar 2008 | 0 | 18 | 1 | 18 | 24.7% | 0.33 [0.01, 7.68] |
| Silva 2008 | 1 | 68 | 0 | 68 | 24.0% | 3.00 [0.12, 72.37] |
| Wigal 2013 | 0 | 44 | 0 | 44 | | Not estimable |
| **Total (95% CI)** | | **870** | | **851** | **100.0%** | **1.62 [0.34, 7.71]** |
| Total events | 4 | | 1 | | | |

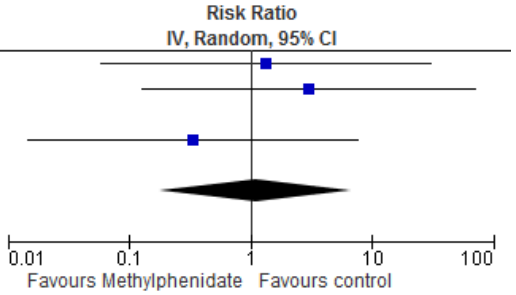
Heterogeneity: Tau² = 0.00; Chi² = 1.64, df = 3 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.61 (P = 0.54)




**6.2 Hallucinations/psychosis**

| Study or Subgroup | Methylphenidate Events | Total | Placebo Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Buitelaar 1995 | 1 | 26 | 0 | 11 | 33.5% | 1.33 [0.06, 30.42] |
| Pelham 1999 | 1 | 21 | 0 | 21 | 33.1% | 3.00 [0.13, 69.70] |
| Pelham 2005 | 0 | 36 | 0 | 36 | | Not estimable |
| Schachar 2008 | 0 | 18 | 1 | 18 | 33.3% | 0.33 [0.01, 7.68] |
| **Total (95% CI)** | | **101** | | **86** | **100.0%** | **1.10 [0.18, 6.72]** |
| Total events | 2 | | 1 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.96, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.10 (P = 0.92)



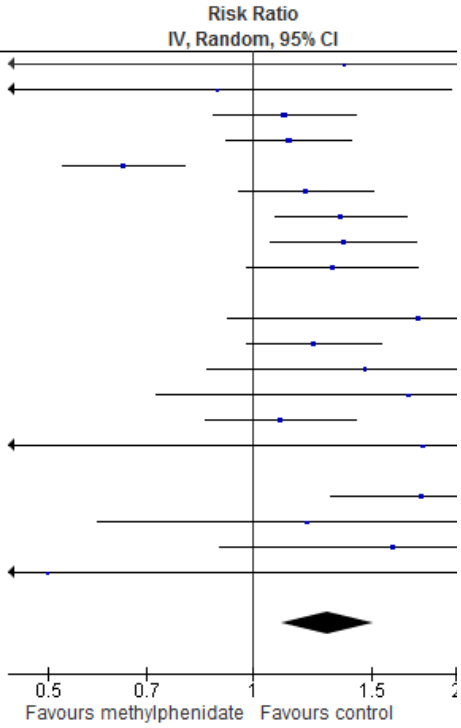

## 7 - Number of non-serious adverse events: parallel-group trials and first-period cross-over trials

**7.1 Total number of non-serious adverse events**

| Study or Subgroup | Methylphenidate Events | Total | Control Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Biederman 2003 | 5 | 65 | 4 | 71 | 1.3% | 1.37 [0.38, 4.87] |
| Carlson 2007 | 5 | 9 | 5 | 8 | 2.7% | 0.89 [0.40, 1.97] |
| Childress 2009 | 116 | 182 | 36 | 63 | 7.2% | 1.12 [0.88, 1.42] |
| Coghill 2013 | 72 | 111 | 63 | 110 | 7.5% | 1.13 [0.92, 1.40] |
| Findling 2006 | 71 | 133 | 38 | 46 | 7.6% | 0.65 [0.53, 0.79] |
| Findling 2008 | 63 | 91 | 49 | 85 | 7.3% | 1.20 [0.96, 1.51] |
| Findling 2010 | 112 | 145 | 40 | 70 | 7.4% | 1.35 [1.08, 1.69] |
| Greenhill 2002 | 80 | 155 | 61 | 161 | 7.1% | 1.36 [1.06, 1.75] |
| Greenhill 2006 | 40 | 53 | 27 | 47 | 6.7% | 1.31 [0.98, 1.76] |
| Jacobi-Polishook 2009 | 0 | 12 | 0 | 12 | | Not estimable |
| Lehmkuhl 2002 | 18 | 43 | 10 | 42 | 3.5% | 1.76 [0.92, 3.35] |
| Newcorn 2008 | 146 | 219 | 40 | 74 | 7.3% | 1.23 [0.98, 1.55] |
| Palumbo 2008 | 17 | 29 | 12 | 30 | 4.3% | 1.47 [0.86, 2.50] |
| Pliszka 2000 | 10 | 20 | 5 | 17 | 2.4% | 1.70 [0.72, 4.01] |
| Riggs 2011 | 70 | 151 | 64 | 152 | 7.1% | 1.10 [0.85, 1.42] |
| Tourette's Syndrome Study Group 2002 | 4 | 37 | 2 | 33 | 0.8% | 1.78 [0.35, 9.12] |
| Tucker 2009 | 47 | 53 | 15 | 56 | 5.1% | 3.31 [2.12, 5.16] |
| Wigal 2004 | 80 | 90 | 21 | 42 | 6.5% | 1.78 [1.30, 2.43] |
| Wilens 2006b | 14 | 87 | 12 | 90 | 3.1% | 1.21 [0.59, 2.46] |
| Wolraich 2001 | 56 | 160 | 10 | 46 | 3.9% | 1.61 [0.89, 2.90] |
| Zeni 2009 | 2 | 16 | 4 | 16 | 0.9% | 0.50 [0.11, 2.35] |
| **Total (95% CI)** | | **1861** | | **1271** | **100.0%** | **1.29 [1.10, 1.51]** |
| Total events | 1028 | | 518 | | | |

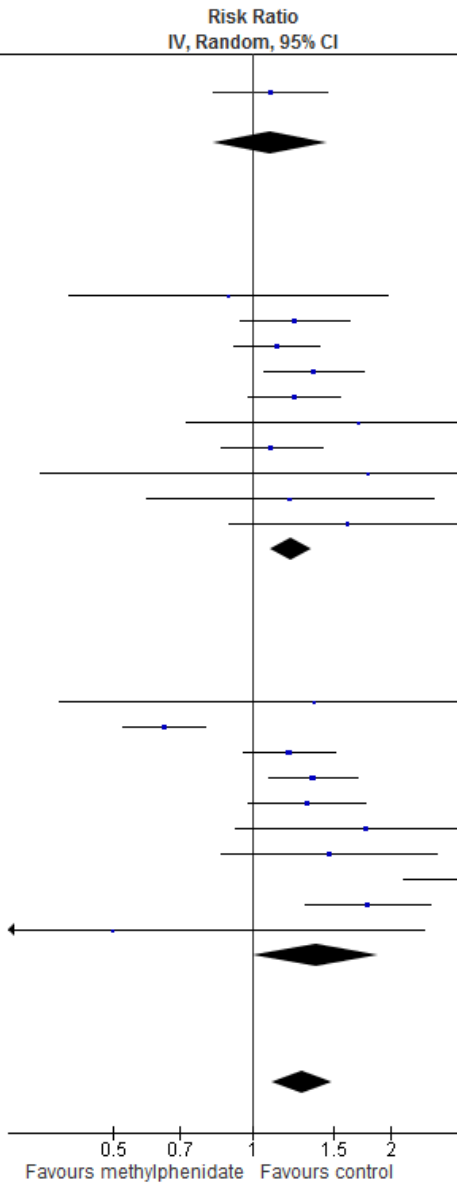
Heterogeneity: Tau² = 0.07; Chi² = 69.75, df = 19 (P < 0.00001); I² = 73%

Test for overall effect: Z = 3.18 (P = 0.001)



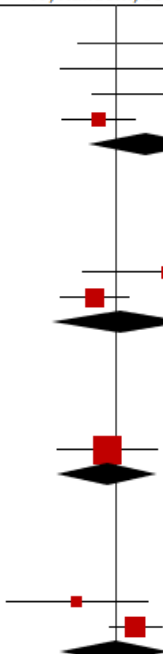
**7.2 Subgroup analysis: total number of non-serious adverse events according to dose**

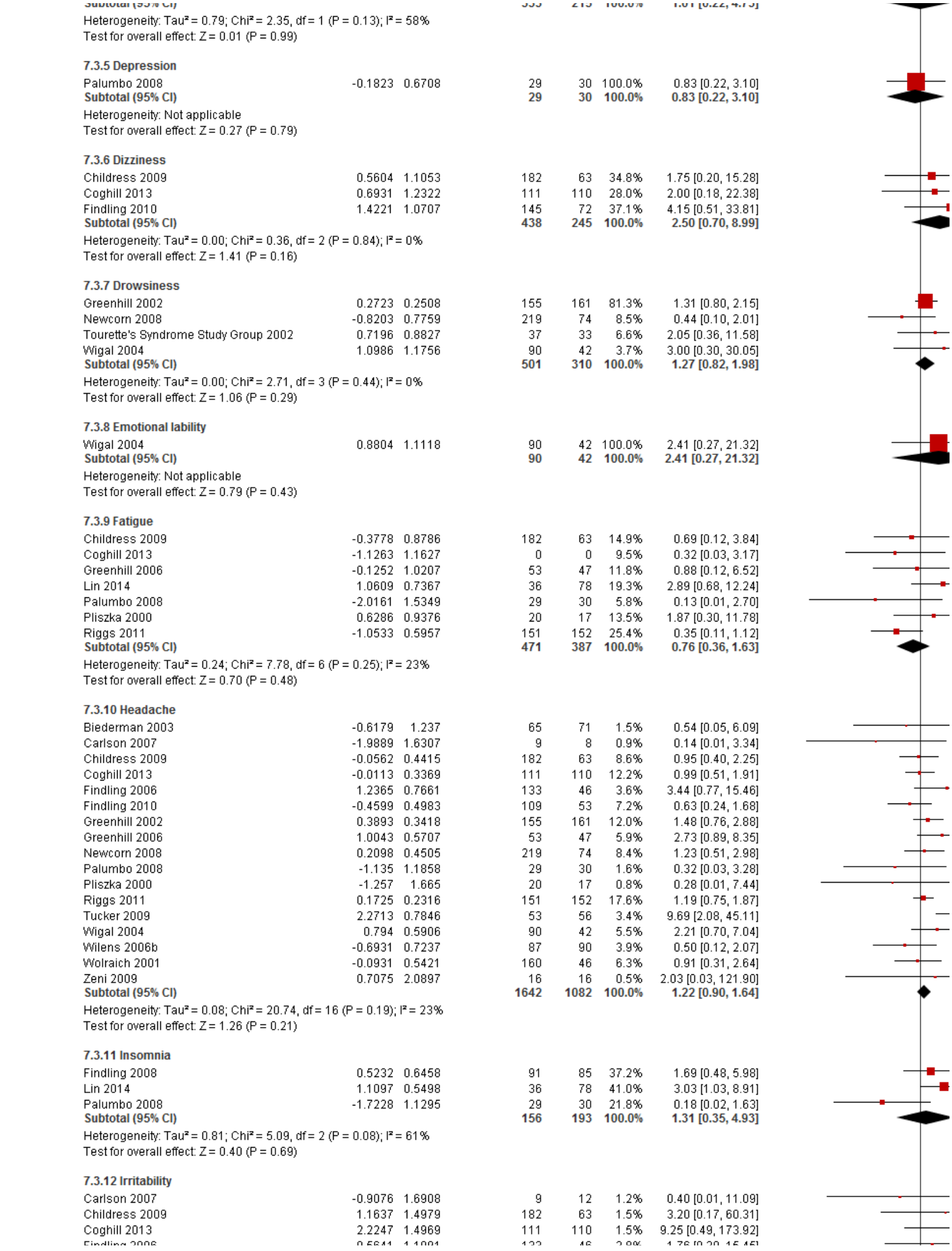
| Study or Subgroup | Methylphenidate Events | Methylphenidate Total | Control Events | Control Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **7.2.1 Low dose** | | | | | | |
| Childress 2009 | 40 | 64 | 36 | 63 | 6.4% | 1.09 [0.82, 1.46] |
| Jacobi-Polishook 2009 | 0 | 12 | 0 | 12 | | Not estimable |
| **Subtotal (95% CI)** | | **76** | | **75** | **6.4%** | **1.09 [0.82, 1.46]** |
| Total events | 40 | | 36 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.61 (P = 0.54) | | | | | | |
| **7.2.2 High dose** | | | | | | |
| Carlson 2007 | 5 | 9 | 5 | 8 | 2.5% | 0.89 [0.40, 1.97] |
| Childress 2009 | 41 | 58 | 36 | 63 | 6.5% | 1.24 [0.94, 1.62] |
| Coghill 2013 | 72 | 111 | 63 | 110 | 7.1% | 1.13 [0.92, 1.40] |
| Greenhill 2002 | 80 | 155 | 61 | 161 | 6.7% | 1.36 [1.06, 1.75] |
| Newcorn 2008 | 146 | 219 | 40 | 74 | 6.9% | 1.23 [0.98, 1.55] |
| Pliszka 2000 | 10 | 20 | 5 | 17 | 2.2% | 1.70 [0.72, 4.01] |
| Riggs 2011 | 70 | 151 | 64 | 152 | 6.7% | 1.10 [0.85, 1.42] |
| Tourette's Syndrome Study Group 2002 | 4 | 37 | 2 | 33 | 0.8% | 1.78 [0.35, 9.12] |
| Wilens 2006b | 14 | 87 | 12 | 90 | 2.9% | 1.21 [0.59, 2.46] |
| Wolraich 2001 | 56 | 160 | 10 | 46 | 3.6% | 1.61 [0.89, 2.90] |
| **Subtotal (95% CI)** | | **1007** | | **754** | **46.0%** | **1.22 [1.10, 1.35]** |
| Total events | 498 | | 298 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 4.12, df = 9 (P = 0.90); I² = 0% | | | | | | |
| Test for overall effect: Z = 3.75 (P = 0.0002) | | | | | | |
| **7.2.3 Unknown dose** | | | | | | |
| Biederman 2003 | 5 | 65 | 4 | 71 | 1.2% | 1.37 [0.38, 4.87] |
| Findling 2006 | 71 | 133 | 38 | 46 | 7.2% | 0.65 [0.53, 0.79] |
| Findling 2008 | 63 | 91 | 49 | 85 | 7.0% | 1.20 [0.96, 1.51] |
| Findling 2010 | 112 | 145 | 40 | 70 | 7.0% | 1.35 [1.08, 1.69] |
| Greenhill 2006 | 40 | 53 | 27 | 47 | 6.3% | 1.31 [0.98, 1.76] |
| Lehmkuhl 2002 | 18 | 43 | 10 | 42 | 3.2% | 1.76 [0.92, 3.35] |
| Palumbo 2008 | 17 | 29 | 12 | 30 | 4.0% | 1.47 [0.86, 2.50] |
| Tucker 2009 | 47 | 53 | 15 | 56 | 4.8% | 3.31 [2.12, 5.16] |
| Wigal 2004 | 80 | 90 | 21 | 42 | 6.1% | 1.78 [1.30, 2.43] |
| Zeni 2009 | 2 | 16 | 4 | 16 | 0.8% | 0.50 [0.11, 2.35] |
| **Subtotal (95% CI)** | | **718** | | **505** | **47.7%** | **1.37 [1.01, 1.87]** |
| Total events | 455 | | 220 | | | |
| Heterogeneity: Tau² = 0.18; Chi² = 65.25, df = 9 (P < 0.00001); I² = 86% | | | | | | |
| Test for overall effect: Z = 2.00 (P = 0.05) | | | | | | |
| **Total (95% CI)** | | **1801** | | **1334** | **100.0%** | **1.28 [1.11, 1.49]** |
| Total events | 993 | | 554 | | | |
| Heterogeneity: Tau² = 0.07; Chi² = 69.85, df = 20 (P < 0.00001); I² = 71% | | | | | | |
| Test for overall effect: Z = 3.30 (P = 0.0010) | | | | | | |
| Test for subgroup differences: Chi² = 1.11, df = 2 (P = 0.57), I² = 0% | | | | | | |




**7.3 Nervous system**

| Study or Subgroup | log[Risk Ratio] | SE | Methylphenidate Total | Control Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **7.3.1 Affective** | | | | | | |
| Findling 2008 | 1.9114 | 1.5194 | 91 | 85 | 18.9% | 6.76 [0.34, 132.87] |
| Greenhill 2006 | 1.5286 | 1.5622 | 53 | 47 | 18.2% | 4.61 [0.22, 98.54] |
| Lin 2014 | 2.368 | 1.5363 | 36 | 78 | 18.6% | 10.68 [0.53, 216.83] |
| Schachar 1997a | -0.4716 | 0.521 | 0 | 0 | 44.2% | 0.62 [0.22, 1.73] |
| **Subtotal (95% CI)** | | | **180** | **210** | **100.0%** | **2.39 [0.48, 11.96]** |
| Heterogeneity: Tau² = 1.25; Chi² = 5.63, df = 3 (P = 0.13); I² = 47% | | | | | | |
| Test for overall effect: Z = 1.06 (P = 0.29) | | | | | | |
| **7.3.2 Aggression** | | | | | | |
| Lin 2014 | 1.4663 | 1.2081 | 36 | 78 | 35.3% | 4.33 [0.41, 46.25] |
| Riggs 2011 | -0.5672 | 0.4902 | 151 | 152 | 64.7% | 0.57 [0.22, 1.48] |
| **Subtotal (95% CI)** | | | **187** | **230** | **100.0%** | **1.16 [0.17, 7.80]** |
| Heterogeneity: Tau² = 1.22; Chi² = 2.43, df = 1 (P = 0.12); I² = 59% | | | | | | |
| Test for overall effect: Z = 0.15 (P = 0.88) | | | | | | |
| **7.3.3 Apathy** | | | | | | |
| Palumbo 2008 | -0.2231 | 0.728 | 29 | 30 | 100.0% | 0.80 [0.19, 3.33] |
| **Subtotal (95% CI)** | | | **29** | **30** | **100.0%** | **0.80 [0.19, 3.33]** |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.31 (P = 0.76) | | | | | | |
| **7.3.4 Confusion** | | | | | | |
| Childress 2009 | -1.0821 | 1.0109 | 182 | 63 | 34.1% | 0.34 [0.05, 2.46] |
| Riggs 2011 | 0.5773 | 0.3849 | 151 | 152 | 65.9% | 1.78 [0.84, 3.79] |
| **Subtotal (95% CI)** | | | **333** | **215** | **100.0%** | **1.01 [0.22, 4.73]** |





Heterogeneity: Tau² = 0.79; Chi² = 2.35, df = 1 (P = 0.13); I² = 58%
Test for overall effect: Z = 0.01 (P = 0.99)

**7.3.5 Depression**

| | | | | | | |
|---|---|---|---|---|---|---|
| Palumbo 2008 | -0.1823 | 0.6708 | 29 | 30 | 100.0% | 0.83 [0.22, 3.10] |
| **Subtotal (95% CI)** | | | **29** | **30** | **100.0%** | **0.83 [0.22, 3.10]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.27 (P = 0.79)

**7.3.6 Dizziness**

| | | | | | | |
|---|---|---|---|---|---|---|
| Childress 2009 | 0.5604 | 1.1053 | 182 | 63 | 34.8% | 1.75 [0.20, 15.28] |
| Coghill 2013 | 0.6931 | 1.2322 | 111 | 110 | 28.0% | 2.00 [0.18, 22.38] |
| Findling 2010 | 1.4221 | 1.0707 | 145 | 72 | 37.1% | 4.15 [0.51, 33.81] |
| **Subtotal (95% CI)** | | | **438** | **245** | **100.0%** | **2.50 [0.70, 8.99]** |

Heterogeneity: Tau² = 0.00; Chi² = 0.36, df = 2 (P = 0.84); I² = 0%
Test for overall effect: Z = 1.41 (P = 0.16)

**7.3.7 Drowsiness**

| | | | | | | |
|---|---|---|---|---|---|---|
| Greenhill 2002 | 0.2723 | 0.2508 | 155 | 161 | 81.3% | 1.31 [0.80, 2.15] |
| Newcorn 2008 | -0.8203 | 0.7759 | 219 | 74 | 8.5% | 0.44 [0.10, 2.01] |
| Tourette's Syndrome Study Group 2002 | 0.7196 | 0.8827 | 37 | 33 | 6.6% | 2.05 [0.36, 11.58] |
| Wigal 2004 | 1.0986 | 1.1756 | 90 | 42 | 3.7% | 3.00 [0.30, 30.05] |
| **Subtotal (95% CI)** | | | **501** | **310** | **100.0%** | **1.27 [0.82, 1.98]** |

Heterogeneity: Tau² = 0.00; Chi² = 2.71, df = 3 (P = 0.44); I² = 0%
Test for overall effect: Z = 1.06 (P = 0.29)

**7.3.8 Emotional lability**

| | | | | | | |
|---|---|---|---|---|---|---|
| Wigal 2004 | 0.8804 | 1.1118 | 90 | 42 | 100.0% | 2.41 [0.27, 21.32] |
| **Subtotal (95% CI)** | | | **90** | **42** | **100.0%** | **2.41 [0.27, 21.32]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)

**7.3.9 Fatigue**

| | | | | | | |
|---|---|---|---|---|---|---|
| Childress 2009 | -0.3778 | 0.8786 | 182 | 63 | 14.9% | 0.69 [0.12, 3.84] |
| Coghill 2013 | -1.1263 | 1.1627 | 0 | 0 | 9.5% | 0.32 [0.03, 3.17] |
| Greenhill 2006 | -0.1252 | 1.0207 | 53 | 47 | 11.8% | 0.88 [0.12, 6.52] |
| Lin 2014 | 1.0609 | 0.7367 | 36 | 78 | 19.3% | 2.89 [0.68, 12.24] |
| Palumbo 2008 | -2.0161 | 1.5349 | 29 | 30 | 5.8% | 0.13 [0.01, 2.70] |
| Pliszka 2000 | 0.6286 | 0.9376 | 20 | 17 | 13.5% | 1.87 [0.30, 11.78] |
| Riggs 2011 | -1.0533 | 0.5957 | 151 | 152 | 25.4% | 0.35 [0.11, 1.12] |
| **Subtotal (95% CI)** | | | **471** | **387** | **100.0%** | **0.76 [0.36, 1.63]** |

Heterogeneity: Tau² = 0.24; Chi² = 7.78, df = 6 (P = 0.25); I² = 23%
Test for overall effect: Z = 0.70 (P = 0.48)

**7.3.10 Headache**

| | | | | | | |
|---|---|---|---|---|---|---|
| Biederman 2003 | -0.6179 | 1.237 | 65 | 71 | 1.5% | 0.54 [0.05, 6.09] |
| Carlson 2007 | -1.9889 | 1.6307 | 9 | 8 | 0.9% | 0.14 [0.01, 3.34] |
| Childress 2009 | -0.0562 | 0.4415 | 182 | 63 | 8.6% | 0.95 [0.40, 2.25] |
| Coghill 2013 | -0.0113 | 0.3369 | 111 | 110 | 12.2% | 0.99 [0.51, 1.91] |
| Findling 2006 | 1.2365 | 0.7661 | 133 | 46 | 3.6% | 3.44 [0.77, 15.46] |
| Findling 2010 | -0.4599 | 0.4983 | 109 | 53 | 7.2% | 0.63 [0.24, 1.68] |
| Greenhill 2002 | 0.3893 | 0.3418 | 155 | 161 | 12.0% | 1.48 [0.76, 2.88] |
| Greenhill 2006 | 1.0043 | 0.5707 | 53 | 47 | 5.9% | 2.73 [0.89, 8.35] |
| Newcorn 2008 | 0.2098 | 0.4505 | 219 | 74 | 8.4% | 1.23 [0.51, 2.98] |
| Palumbo 2008 | -1.135 | 1.1858 | 29 | 30 | 1.6% | 0.32 [0.03, 3.28] |
| Pliszka 2000 | -1.257 | 1.665 | 20 | 17 | 0.8% | 0.28 [0.01, 7.44] |
| Riggs 2011 | 0.1725 | 0.2316 | 151 | 152 | 17.6% | 1.19 [0.75, 1.87] |
| Tucker 2009 | 2.2713 | 0.7846 | 53 | 56 | 3.4% | 9.69 [2.08, 45.11] |
| Wigal 2004 | 0.794 | 0.5906 | 90 | 42 | 5.5% | 2.21 [0.70, 7.04] |
| Wilens 2006b | -0.6931 | 0.7237 | 87 | 90 | 3.9% | 0.50 [0.12, 2.07] |
| Wolraich 2001 | -0.0931 | 0.5421 | 160 | 46 | 6.3% | 0.91 [0.31, 2.64] |
| Zeni 2009 | 0.7075 | 2.0897 | 16 | 16 | 0.5% | 2.03 [0.03, 121.90] |
| **Subtotal (95% CI)** | | | **1642** | **1082** | **100.0%** | **1.22 [0.90, 1.64]** |

Heterogeneity: Tau² = 0.08; Chi² = 20.74, df = 16 (P = 0.19); I² = 23%
Test for overall effect: Z = 1.26 (P = 0.21)

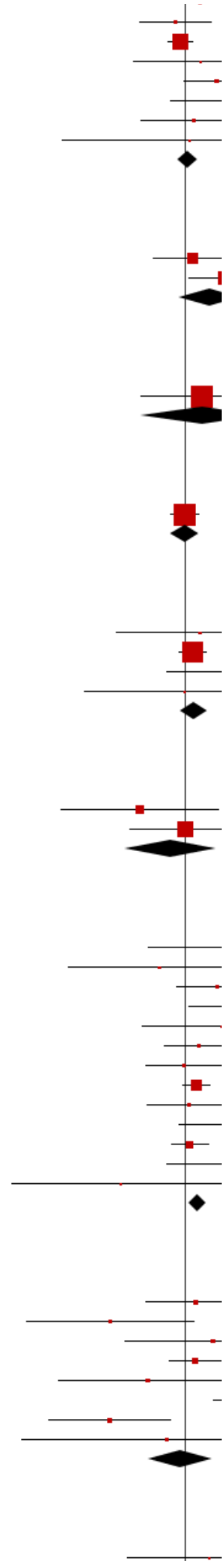
**7.3.11 Insomnia**

| | | | | | | |
|---|---|---|---|---|---|---|
| Findling 2008 | 0.5232 | 0.6458 | 91 | 85 | 37.2% | 1.69 [0.48, 5.98] |
| Lin 2014 | 1.1097 | 0.5498 | 36 | 78 | 41.0% | 3.03 [1.03, 8.91] |
| Palumbo 2008 | -1.7228 | 1.1295 | 29 | 30 | 21.8% | 0.18 [0.02, 1.63] |
| **Subtotal (95% CI)** | | | **156** | **193** | **100.0%** | **1.31 [0.35, 4.93]** |

Heterogeneity: Tau² = 0.81; Chi² = 5.09, df = 2 (P = 0.08); I² = 61%
Test for overall effect: Z = 0.40 (P = 0.69)

**7.3.12 Irritability**

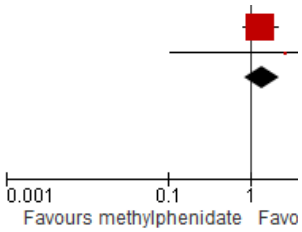
| | | | | | | |
|---|---|---|---|---|---|---|
| Carlson 2007 | -0.9076 | 1.6908 | 9 | 12 | 1.2% | 0.40 [0.01, 11.09] |
| Childress 2009 | 1.1637 | 1.4979 | 182 | 63 | 1.5% | 3.20 [0.17, 60.31] |
| Coghill 2013 | 2.2247 | 1.4969 | 111 | 110 | 1.5% | 9.25 [0.49, 173.92] |



| | | | | | | |
|---|---|---|---|---|---|---|
| Findling 2006 | 0.5641 | 1.1091 | 133 | 46 | 2.8% | 1.76 [0.20, 15.45] |
| Findling 2010 | -0.3374 | 0.6684 | 109 | 53 | 7.6% | 0.71 [0.19, 2.64] |
| Greenhill 2002 | -0.1569 | 0.2256 | 155 | 161 | 66.9% | 0.85 [0.55, 1.33] |
| Greenhill 2006 | 0.59 | 1.2415 | 53 | 47 | 2.2% | 1.80 [0.16, 20.56] |
| Lin 2014 | 1.1787 | 0.6132 | 36 | 78 | 9.1% | 3.25 [0.98, 10.81] |
| Newcorn 2008 | 1.5275 | 1.0466 | 219 | 74 | 3.1% | 4.61 [0.59, 35.83] |
| Pliszka 2000 | 0.3448 | 0.9771 | 20 | 18 | 3.6% | 1.41 [0.21, 9.58] |
| Zeni 2009 | 0.1995 | 2.382 | 16 | 16 | 0.6% | 1.22 [0.01, 130.08] |
| **Subtotal (95% CI)** | | | **1043** | **678** | **100.0%** | **1.11 [0.77, 1.60]** |
| Heterogeneity: Tau² = 0.00; Chi² = 9.95, df = 10 (P = 0.45); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.58 (P = 0.56) | | | | | | |
| **7.3.13 Nervousness** | | | | | | |
| Palumbo 2008 | 0.3032 | 0.7281 | 29 | 30 | 46.3% | 1.35 [0.33, 5.64] |
| Riggs 2011 | 1.4558 | 0.6562 | 151 | 152 | 53.7% | 4.29 [1.18, 15.52] |
| **Subtotal (95% CI)** | | | **180** | **182** | **100.0%** | **2.52 [0.82, 7.76]** |
| Heterogeneity: Tau² = 0.18; Chi² = 1.38, df = 1 (P = 0.24); I² = 28% | | | | | | |
| Test for overall effect: Z = 1.61 (P = 0.11) | | | | | | |
| **7.3.14 Pain** | | | | | | |
| Wigal 2004 | 0.6455 | 1.134 | 90 | 42 | 100.0% | 1.91 [0.21, 17.60] |
| **Subtotal (95% CI)** | | | **90** | **42** | **100.0%** | **1.91 [0.21, 17.60]** |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.57 (P = 0.57) | | | | | | |
| **7.3.15 Picking at skin or fingers, nail biting, lip or cheek chewing** | | | | | | |
| Greenhill 2002 | 0.0148 | 0.2645 | 155 | 161 | 100.0% | 1.01 [0.60, 1.70] |
| **Subtotal (95% CI)** | | | **155** | **161** | **100.0%** | **1.01 [0.60, 1.70]** |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.06 (P = 0.96) | | | | | | |
| **7.3.16 Sad, tearful or depressed** | | | | | | |
| Childress 2009 | 0.5647 | 1.556 | 182 | 63 | 2.6% | 1.76 [0.08, 37.13] |
| Greenhill 2002 | 0.284 | 0.2585 | 155 | 161 | 93.0% | 1.33 [0.80, 2.20] |
| Lin 2014 | 2.368 | 1.5363 | 36 | 78 | 2.6% | 10.68 [0.53, 216.83] |
| Zeni 2009 | 0.0219 | 1.873 | 16 | 16 | 1.8% | 1.02 [0.03, 40.16] |
| **Subtotal (95% CI)** | | | **389** | **318** | **100.0%** | **1.41 [0.86, 2.29]** |
| Heterogeneity: Tau² = 0.00; Chi² = 1.84, df = 3 (P = 0.61); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.37 (P = 0.17) | | | | | | |
| **7.3.17 Somnolence** | | | | | | |
| Lin 2014 | -1.6394 | 1.4636 | 36 | 78 | 33.4% | 0.19 [0.01, 3.42] |
| Palumbo 2008 | 0.0364 | 1.0357 | 29 | 30 | 66.6% | 1.04 [0.14, 7.90] |
| **Subtotal (95% CI)** | | | **65** | **108** | **100.0%** | **0.59 [0.11, 3.11]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 1 (P = 0.35); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.62 (P = 0.54) | | | | | | |
| **7.3.18 Trouble sleeping or sleep problems** | | | | | | |
| Biederman 2003 | 1.7281 | 1.5588 | 65 | 71 | 1.2% | 5.63 [0.27, 119.50] |
| Carlson 2007 | -0.9076 | 1.6908 | 9 | 12 | 1.0% | 0.40 [0.01, 11.09] |
| Childress 2009 | 1.2082 | 0.7603 | 182 | 63 | 4.9% | 3.35 [0.75, 14.86] |
| Coghill 2013 | 3.0196 | 1.4574 | 111 | 110 | 1.3% | 20.48 [1.18, 356.40] |
| Findling 2006 | 1.3814 | 1.487 | 133 | 46 | 1.3% | 3.98 [0.22, 73.40] |
| Findling 2008 | 0.5232 | 0.6458 | 91 | 85 | 6.8% | 1.69 [0.48, 5.98] |
| Findling 2010 | -0.0072 | 0.7223 | 145 | 72 | 5.5% | 0.99 [0.24, 4.09] |
| Greenhill 2002 | 0.4327 | 0.2529 | 155 | 161 | 44.6% | 1.54 [0.94, 2.53] |
| Greenhill 2006 | 0.1801 | 0.7915 | 53 | 47 | 4.6% | 1.20 [0.25, 5.65] |
| Newcorn 2008 | 1.8154 | 1.038 | 219 | 74 | 2.6% | 6.14 [0.80, 46.99] |
| Riggs 2011 | 0.1845 | 0.344 | 151 | 152 | 24.1% | 1.20 [0.61, 2.36] |
| Wilens 2006b | 2.278 | 1.498 | 87 | 90 | 1.3% | 9.76 [0.52, 183.83] |
| Zeni 2009 | -2.304 | 2.035 | 16 | 16 | 0.7% | 0.10 [0.00, 5.39] |
| **Subtotal (95% CI)** | | | **1417** | **999** | **100.0%** | **1.60 [1.15, 2.23]** |
| Heterogeneity: Tau² = 0.00; Chi² = 11.98, df = 12 (P = 0.45); I² = 0% | | | | | | |
| Test for overall effect: Z = 2.79 (P = 0.005) | | | | | | |
| **7.3.19 Tics or nervous movements** | | | | | | |
| Coghill 2013 | 0.4055 | 0.923 | 111 | 110 | 15.0% | 1.50 [0.25, 9.16] |
| Findling 2006 | -2.7081 | 1.5588 | 133 | 46 | 9.1% | 0.07 [0.00, 1.41] |
| Findling 2008 | 1.0418 | 1.6399 | 91 | 85 | 8.5% | 2.83 [0.11, 70.52] |
| Greenhill 2002 | 0.3791 | 0.4789 | 155 | 161 | 20.1% | 1.46 [0.57, 3.73] |
| Pliszka 2000 | -1.3282 | 1.6681 | 19 | 16 | 8.4% | 0.26 [0.01, 6.97] |
| Schachar 1997a | 1.554 | 0.2474 | 37 | 29 | 22.1% | 4.73 [2.91, 7.68] |
| Wolraich 2001 | -2.7175 | 1.1314 | 160 | 46 | 12.7% | 0.07 [0.01, 0.61] |
| Zeni 2009 | -0.6349 | 2.7003 | 16 | 16 | 4.1% | 0.53 [0.00, 105.38] |
| **Subtotal (95% CI)** | | | **722** | **509** | **100.0%** | **0.85 [0.26, 2.79]** |
| Heterogeneity: Tau² = 1.59; Chi² = 25.88, df = 7 (P = 0.0005); I² = 73% | | | | | | |
| Test for overall effect: Z = 0.26 (P = 0.79) | | | | | | |
| **7.3.20 Worried or anxious** | | | | | | |
| Childress 2009 | 0.9068 | 1.5189 | 182 | 63 | 2.8% | 2.48 [0.13, 48.61] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Greenhill 2002 | 0.284 | 0.2585 | 155 | 161 | 95.0% | 1.33 [0.80, 2.20] | |
| Pliszka 2000 | 0.9842 | 1.6677 | 19 | 16 | 2.3% | 2.68 [0.10, 70.30] | |
| **Subtotal (95% CI)** | | | **356** | **240** | **100.0%** | **1.37 [0.84, 2.25]** | |

Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 2 (P = 0.85); I² = 0%
Test for overall effect: Z = 1.26 (P = 0.21)




Test for subgroup differences: Chi² = 10.92, df = 19 (P = 0.93), I² = 0%

**7.4 Digestive system**

| Study or Subgroup | Methylphenidate Events | Total | Control Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **7.4.1 Decreased appetite** | | | | | | |
| Biederman 2003 | 2 | 65 | 0 | 71 | 1.3% | 5.45 [0.27, 111.54] |
| Childress 2009 | 22 | 182 | 3 | 63 | 6.9% | 2.54 [0.79, 8.19] |
| Coghill 2013 | 17 | 111 | 3 | 110 | 6.7% | 5.62 [1.69, 18.62] |
| Findling 2006 | 3 | 133 | 0 | 46 | 1.4% | 2.46 [0.13, 46.65] |
| Findling 2008 | 17 | 91 | 4 | 85 | 8.1% | 3.97 [1.39, 11.32] |
| Findling 2010 | 37 | 145 | 1 | 72 | 2.9% | 18.37 [2.57, 131.23] |
| Greenhill 2002 | 73 | 155 | 33 | 161 | 21.8% | 2.30 [1.62, 3.25] |
| Greenhill 2006 | 16 | 53 | 4 | 47 | 8.4% | 3.55 [1.28, 9.87] |
| Lin 2014 | 17 | 36 | 3 | 78 | 7.0% | 12.28 [3.84, 39.25] |
| Newcorn 2008 | 37 | 219 | 2 | 74 | 5.3% | 6.25 [1.54, 25.31] |
| Pliszka 2000 | 3 | 20 | 0 | 18 | 1.4% | 6.33 [0.35, 114.81] |
| Riggs 2011 | 25 | 151 | 9 | 152 | 12.8% | 2.80 [1.35, 5.79] |
| Tucker 2009 | 20 | 53 | 0 | 56 | 1.6% | 43.28 [2.68, 698.02] |
| Wigal 2004 | 9 | 90 | 0 | 42 | 1.5% | 8.98 [0.53, 150.71] |
| Wilens 2006b | 2 | 87 | 0 | 90 | 1.3% | 5.17 [0.25, 106.18] |
| Wolraich 2001 | 33 | 160 | 6 | 46 | 11.4% | 1.58 [0.71, 3.54] |
| **Subtotal (95% CI)** | | **1751** | | **1211** | **100.0%** | **3.66 [2.56, 5.23]** |
| Total events | 333 | | 68 | | | |
| Heterogeneity: Tau² = 0.12; Chi² = 20.88, df = 15 (P = 0.14); I² = 28% | | | | | | |
| Test for overall effect: Z = 7.13 (P < 0.00001) | | | | | | |
| **7.4.2 Decreased weight** | | | | | | |
| Carlson 2007 | 1 | 8 | 1 | 9 | 14.8% | 1.13 [0.08, 15.19] |
| Childress 2009 | 4 | 182 | 0 | 63 | 11.8% | 3.15 [0.17, 57.65] |
| Coghill 2013 | 5 | 111 | 0 | 110 | 12.0% | 10.90 [0.61, 194.82] |
| Findling 2008 | 7 | 91 | 0 | 85 | 12.3% | 14.02 [0.81, 241.82] |
| Lin 2014 | 4 | 36 | 0 | 78 | 11.9% | 19.22 [1.06, 347.68] |
| Wigal 2004 | 4 | 44 | 2 | 42 | 37.0% | 1.91 [0.37, 9.88] |
| **Subtotal (95% CI)** | | **472** | | **387** | **100.0%** | **3.89 [1.43, 10.59]** |
| Total events | 25 | | 3 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 4.05, df = 5 (P = 0.54); I² = 0% | | | | | | |
| Test for overall effect: Z = 2.66 (P = 0.008) | | | | | | |
| **7.4.3 Diarrhoea** | | | | | | |
| Childress 2009 | 6 | 182 | 2 | 63 | 36.0% | 1.04 [0.22, 5.01] |
| Coghill 2013 | 2 | 111 | 3 | 110 | 28.5% | 0.66 [0.11, 3.88] |
| Greenhill 2006 | 2 | 53 | 1 | 47 | 15.9% | 1.77 [0.17, 18.94] |
| Lin 2014 | 0 | 36 | 2 | 78 | 9.8% | 0.43 [0.02, 8.67] |
| Wilens 2006b | 2 | 87 | 0 | 90 | 9.8% | 5.17 [0.25, 106.18] |
| **Subtotal (95% CI)** | | **469** | | **388** | **100.0%** | **1.07 [0.41, 2.74]** |
| Total events | 12 | | 8 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 1.86, df = 4 (P = 0.76); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.13 (P = 0.90) | | | | | | |
| **7.4.4 Dyspepsia** | | | | | | |
| Greenhill 2006 | 4 | 53 | 2 | 47 | 31.4% | 1.77 [0.34, 9.25] |
| Palumbo 2008 | 7 | 29 | 4 | 30 | 68.6% | 1.81 [0.59, 5.53] |
| **Subtotal (95% CI)** | | **82** | | **77** | **100.0%** | **1.80 [0.71, 4.54]** |
| Total events | 11 | | 6 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.24 (P = 0.21) | | | | | | |
| **7.4.5 Increased appetite** | | | | | | |
| Findling 2006 | 0 | 133 | 2 | 46 | 100.0% | 0.07 [0.00, 1.43] |
| **Subtotal (95% CI)** | | **133** | | **46** | **100.0%** | **0.07 [0.00, 1.43]** |
| Total events | 0 | | 2 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.73 (P = 0.08) | | | | | | |
| **7.4.6 Nausea** | | | | | | |
| Carlson 2007 | 0 | 9 | 1 | 8 | 1.9% | 0.30 [0.01, 6.47] |
| Childress 2009 | 10 | 182 | 5 | 63 | 14.4% | 0.69 [0.25, 1.95] |
| Coghill 2013 | 8 | 111 | 3 | 110 | 9.7% | 2.64 [0.72, 9.70] |
| Findling 2008 | 7 | 91 | 2 | 85 | 7.1% | 3.27 [0.70, 15.30] |

| | | | | | | |
|---|---|---|---|---|---|---|
| Findling 2010 | 14 | 145 | 2 | 72 | 7.9% | 3.48 [0.81, 14.88] |
| Greenhill 2006 | 6 | 53 | 3 | 47 | 9.3% | 1.77 [0.47, 6.70] |
| Lin 2014 | 3 | 36 | 4 | 78 | 8.0% | 1.63 [0.38, 6.89] |
| Newcorn 2008 | 13 | 219 | 6 | 74 | 17.2% | 0.73 [0.29, 1.86] |
| Riggs 2011 | 8 | 151 | 9 | 152 | 17.3% | 0.89 [0.35, 2.26] |
| Wigal 2004 | 10 | 90 | 1 | 42 | 4.2% | 4.67 [0.62, 35.28] |
| Wilens 2006b | 1 | 87 | 2 | 90 | 3.1% | 0.52 [0.05, 5.60] |
| **Subtotal (95% CI)** | | **1174** | | **821** | **100.0%** | **1.30 [0.85, 1.99]** |
| Total events | 80 | | 38 | | | |

Heterogeneity: Tau² = 0.05; Chi² = 11.06, df = 10 (P = 0.35); I² = 10%
Test for overall effect: Z = 1.21 (P = 0.22)

**7.4.7 Stomachache**

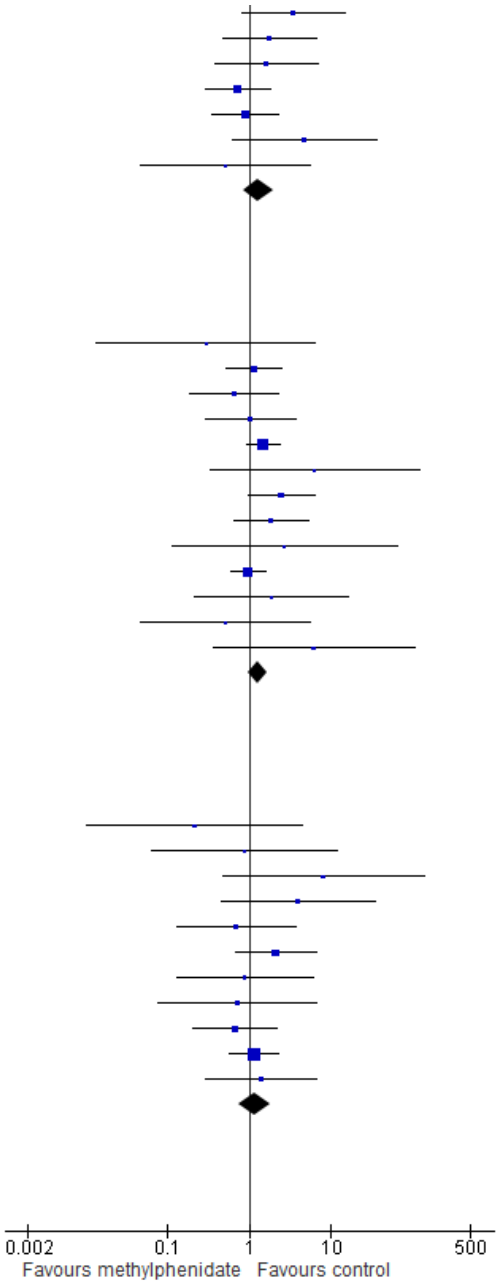
| | | | | | | |
|---|---|---|---|---|---|---|
| Carlson 2007 | 0 | 9 | 1 | 8 | 0.7% | 0.30 [0.01, 6.47] |
| Childress 2009 | 23 | 182 | 7 | 63 | 10.9% | 1.14 [0.51, 2.52] |
| Coghill 2013 | 4 | 111 | 6 | 110 | 4.5% | 0.66 [0.19, 2.28] |
| Findling 2006 | 9 | 133 | 3 | 46 | 4.3% | 1.04 [0.29, 3.67] |
| Greenhill 2002 | 36 | 155 | 25 | 161 | 32.6% | 1.50 [0.94, 2.37] |
| Greenhill 2006 | 3 | 53 | 0 | 47 | 0.8% | 6.22 [0.33, 117.41] |
| Lin 2014 | 8 | 36 | 7 | 78 | 7.9% | 2.48 [0.97, 6.30] |
| Newcorn 2008 | 22 | 219 | 4 | 74 | 6.5% | 1.86 [0.66, 5.22] |
| Pliszka 2000 | 1 | 20 | 0 | 18 | 0.7% | 2.71 [0.12, 62.70] |
| Riggs 2011 | 25 | 151 | 26 | 152 | 27.5% | 0.97 [0.59, 1.60] |
| Wigal 2004 | 4 | 90 | 1 | 42 | 1.5% | 1.87 [0.22, 16.19] |
| Wilens 2006b | 1 | 87 | 2 | 90 | 1.2% | 0.52 [0.05, 5.60] |
| Wolraich 2001 | 10 | 160 | 0 | 46 | 0.9% | 6.13 [0.37, 102.68] |
| **Subtotal (95% CI)** | | **1406** | | **935** | **100.0%** | **1.30 [1.00, 1.69]** |
| Total events | 146 | | 82 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 9.38, df = 12 (P = 0.67); I² = 0%
Test for overall effect: Z = 1.95 (P = 0.05)

**7.4.8 Vomiting**

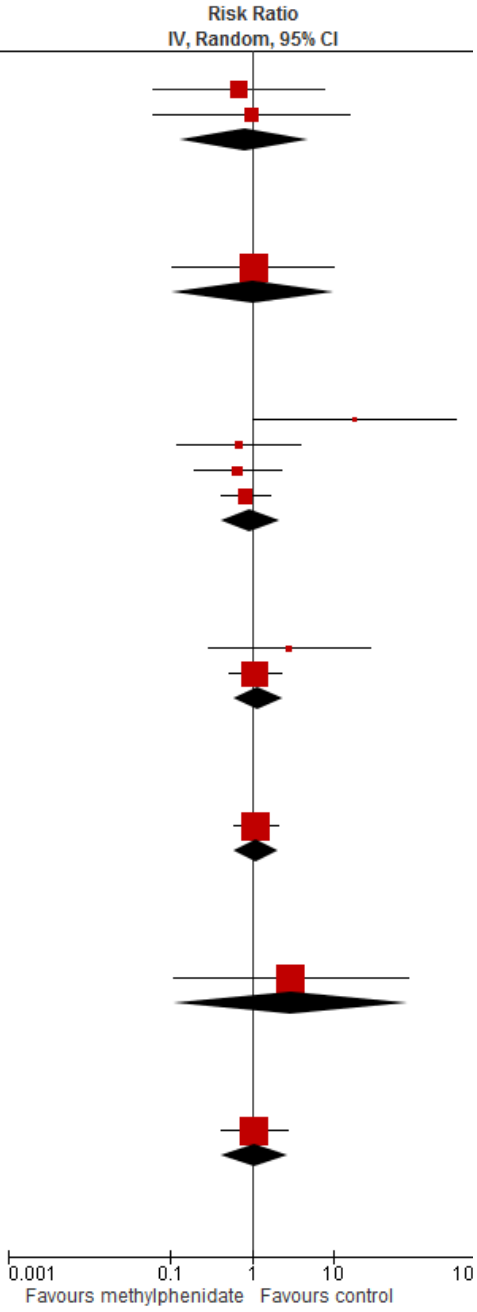
| | | | | | | |
|---|---|---|---|---|---|---|
| Biederman 2003 | 0 | 65 | 2 | 71 | 2.0% | 0.22 [0.01, 4.46] |
| Carlson 2007 | 1 | 9 | 1 | 8 | 2.7% | 0.89 [0.07, 12.00] |
| Childress 2009 | 11 | 182 | 0 | 63 | 2.3% | 8.04 [0.48, 134.55] |
| Coghill 2013 | 4 | 111 | 1 | 110 | 3.8% | 3.96 [0.45, 34.90] |
| Findling 2006 | 4 | 133 | 2 | 46 | 6.6% | 0.69 [0.13, 3.65] |
| Findling 2008 | 9 | 91 | 4 | 85 | 14.0% | 2.10 [0.67, 6.57] |
| Greenhill 2006 | 2 | 53 | 2 | 47 | 4.9% | 0.89 [0.13, 6.05] |
| Lin 2014 | 1 | 36 | 3 | 78 | 3.7% | 0.72 [0.08, 6.71] |
| Newcorn 2008 | 8 | 219 | 4 | 74 | 13.3% | 0.68 [0.21, 2.18] |
| Riggs 2011 | 16 | 151 | 14 | 152 | 39.2% | 1.15 [0.58, 2.27] |
| Wigal 2004 | 6 | 90 | 2 | 42 | 7.5% | 1.40 [0.29, 6.65] |
| **Subtotal (95% CI)** | | **1140** | | **776** | **100.0%** | **1.17 [0.76, 1.79]** |
| Total events | 62 | | 35 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 6.79, df = 10 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.72 (P = 0.47)



**7.5 Circulatory and respiratory systems**

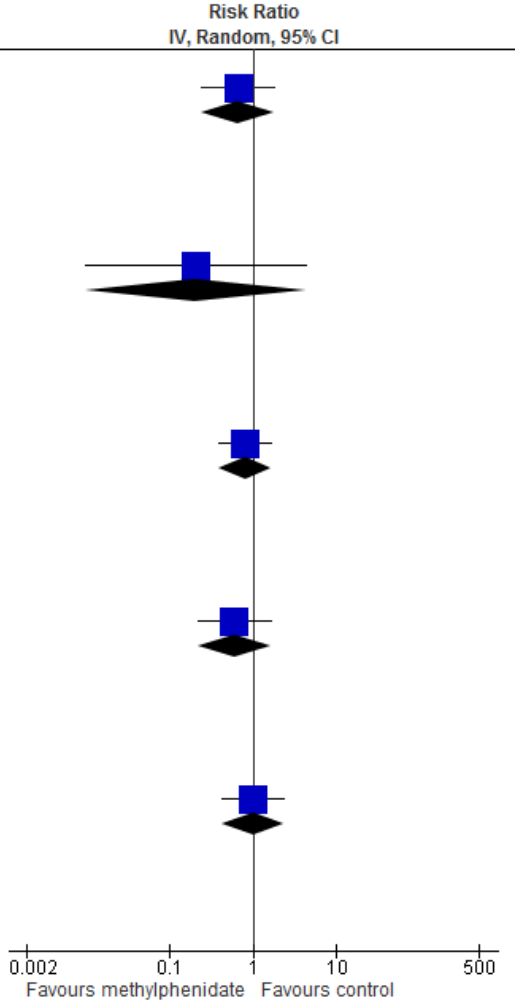
| Study or Subgroup | log[Risk Ratio] | SE | Methylphenidate Total | Control Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **7.5.1 ECG: prolonged QT-interval** | | | | | | |
| Childress 2009 | -0.3727 | 1.2336 | 182 | 63 | 57.0% | 0.69 [0.06, 7.73] |
| Coghill 2013 | -0.0091 | 1.4207 | 111 | 110 | 43.0% | 0.99 [0.06, 16.05] |
| **Subtotal (95% CI)** | | | **293** | **173** | **100.0%** | **0.81 [0.13, 5.00]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.23 (P = 0.82) | | | | | | |
| **7.5.2 ECG: tachycardia** | | | | | | |
| Childress 2009 | 0.0384 | 1.1641 | 182 | 63 | 100.0% | 1.04 [0.11, 10.18] |
| **Subtotal (95% CI)** | | | **182** | **63** | **100.0%** | **1.04 [0.11, 10.18]** |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.03 (P = 0.97) | | | | | | |
| **7.5.3 Cough** | | | | | | |
| Coghill 2013 | 2.8987 | 1.4616 | 111 | 110 | 7.5% | 18.15 [1.03, 318.42] |
| Findling 2006 | -0.3825 | 0.8834 | 133 | 46 | 17.4% | 0.68 [0.12, 3.85] |
| Newcorn 2008 | -0.4102 | 0.6277 | 219 | 74 | 27.9% | 0.66 [0.19, 2.27] |
| Riggs 2011 | -0.1868 | 0.3606 | 151 | 152 | 47.1% | 0.83 [0.41, 1.68] |
| **Subtotal (95% CI)** | | | **614** | **382** | **100.0%** | **0.95 [0.41, 2.18]** |
| Heterogeneity: Tau² = 0.25; Chi² = 4.60, df = 3 (P = 0.20); I² = 35% | | | | | | |
| Test for overall effect: Z = 0.12 (P = 0.91) | | | | | | |
| **7.5.4 Nasal congestion** | | | | | | |
| Findling 2008 | 1.0521 | 1.1647 | 91 | 85 | 9.6% | 2.86 [0.29, 28.07] |
| Riggs 2011 | 0.0792 | 0.3793 | 151 | 152 | 90.4% | 1.08 [0.51, 2.28] |
| **Subtotal (95% CI)** | | | **242** | **237** | **100.0%** | **1.19 [0.59, 2.41]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.63, df = 1 (P = 0.43); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.48 (P = 0.63) | | | | | | |
| **7.5.5 Pharyngolaryngeal pain** | | | | | | |
| Riggs 2011 | 0.1141 | 0.3264 | 151 | 152 | 100.0% | 1.12 [0.59, 2.13] |
| **Subtotal (95% CI)** | | | **151** | **152** | **100.0%** | **1.12 [0.59, 2.13]** |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.35 (P = 0.73) | | | | | | |
| **7.5.6 Supraventricular extrasystoles** | | | | | | |
| Carlson 2007 | 1.0986 | 1.7035 | 9 | 8 | 100.0% | 3.00 [0.11, 84.55] |
| **Subtotal (95% CI)** | | | **9** | **8** | **100.0%** | **3.00 [0.11, 84.55]** |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.64 (P = 0.52) | | | | | | |
| **7.5.7 Upper respiratory tract infection** | | | | | | |
| Findling 2010 | 0.069 | 0.4823 | 145 | 72 | 100.0% | 1.07 [0.42, 2.76] |
| **Subtotal (95% CI)** | | | **145** | **72** | **100.0%** | **1.07 [0.42, 2.76]** |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.14 (P = 0.89) | | | | | | |




Test for subgroup differences: Chi² = 0.63, df = 6 (P = 1.00), I² = 0%

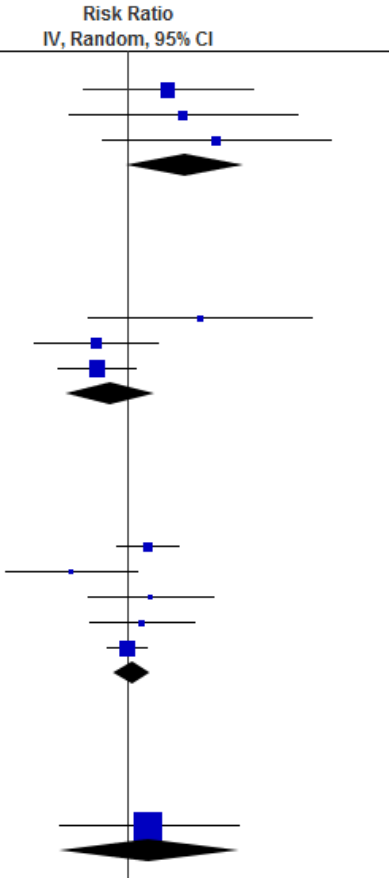
### 7.6 Skeletal and muscular systems

| Study or Subgroup | Methylphenidate Events | Total | Control Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **7.6.1 Arthralgia** | | | | | | |
| Riggs 2011 | 6 | 151 | 9 | 152 | 100.0% | 0.67 [0.24, 1.84] |
| **Subtotal (95% CI)** | | **151** | | **152** | **100.0%** | **0.67 [0.24, 1.84]** |
| Total events | 6 | | 9 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.78 (P = 0.44) | | | | | | |
| **7.6.2 Asthenia** | | | | | | |
| Wilens 2006b | 0 | 87 | 2 | 90 | 100.0% | 0.21 [0.01, 4.25] |
| **Subtotal (95% CI)** | | **87** | | **90** | **100.0%** | **0.21 [0.01, 4.25]** |
| Total events | 0 | | 2 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.02 (P = 0.31) | | | | | | |
| **7.6.3 Back pain** | | | | | | |
| Riggs 2011 | 12 | 151 | 15 | 152 | 100.0% | 0.81 [0.39, 1.66] |
| **Subtotal (95% CI)** | | **151** | | **152** | **100.0%** | **0.81 [0.39, 1.66]** |
| Total events | 12 | | 15 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.59 (P = 0.56) | | | | | | |
| **7.6.4 Myalgia** | | | | | | |
| Riggs 2011 | 6 | 151 | 10 | 152 | 100.0% | 0.60 [0.23, 1.62] |
| **Subtotal (95% CI)** | | **151** | | **152** | **100.0%** | **0.60 [0.23, 1.62]** |
| Total events | 6 | | 10 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.00 (P = 0.32) | | | | | | |
| **7.6.5 Toothache** | | | | | | |
| Riggs 2011 | 10 | 151 | 10 | 152 | 100.0% | 1.01 [0.43, 2.35] |
| **Subtotal (95% CI)** | | **151** | | **152** | **100.0%** | **1.01 [0.43, 2.35]** |
| Total events | 10 | | 10 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.02 (P = 0.99) | | | | | | |




### 7.7 Immune system

| Study or Subgroup | Methylphenidate Events | Total | Control Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **7.7.1 Gastroenteritis** | | | | | | |
| Coghill 2013 | 3 | 111 | 1 | 110 | 47.3% | 2.97 [0.31, 28.14] |
| Greenhill 2006 | 2 | 53 | 0 | 47 | 26.4% | 4.44 [0.22, 90.29] |
| Lin 2014 | 2 | 36 | 0 | 78 | 26.4% | 10.68 [0.53, 216.83] |
| **Subtotal (95% CI)** | | **200** | | **235** | **100.0%** | **4.63 [0.99, 21.72]** |
| Total events | 7 | | 1 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.45, df = 2 (P = 0.80); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.94 (P = 0.05) | | | | | | |
| **7.7.2 Influenza** | | | | | | |
| Coghill 2013 | 3 | 111 | 0 | 110 | 13.4% | 6.94 [0.36, 132.75] |
| Greenhill 2006 | 2 | 53 | 4 | 47 | 32.6% | 0.44 [0.09, 2.31] |
| Riggs 2011 | 5 | 151 | 11 | 152 | 54.0% | 0.46 [0.16, 1.29] |
| **Subtotal (95% CI)** | | **315** | | **309** | **100.0%** | **0.65 [0.20, 2.10]** |
| Total events | 10 | | 15 | | | |
| Heterogeneity: Tau² = 0.38; Chi² = 3.02, df = 2 (P = 0.22); I² = 34% | | | | | | |
| Test for overall effect: Z = 0.72 (P = 0.47) | | | | | | |
| **7.7.3 Nasopharyngitis** | | | | | | |
| Coghill 2013 | 14 | 111 | 8 | 110 | 26.3% | 1.73 [0.76, 3.97] |
| Findling 2006 | 2 | 133 | 3 | 46 | 7.2% | 0.23 [0.04, 1.34] |
| Findling 2008 | 4 | 91 | 2 | 85 | 7.9% | 1.87 [0.35, 9.94] |
| Greenhill 2006 | 5 | 53 | 3 | 47 | 11.3% | 1.48 [0.37, 5.85] |
| Riggs 2011 | 23 | 151 | 23 | 152 | 47.2% | 1.01 [0.59, 1.71] |
| **Subtotal (95% CI)** | | **539** | | **440** | **100.0%** | **1.15 [0.70, 1.87]** |
| Total events | 48 | | 39 | | | |
| Heterogeneity: Tau² = 0.06; Chi² = 4.85, df = 4 (P = 0.30); I² = 17% | | | | | | |
| Test for overall effect: Z = 0.54 (P = 0.59) | | | | | | |
| **7.7.4 Otitis media** | | | | | | |
| Greenhill 2006 | 2 | 53 | 1 | 47 | 100.0% | 1.77 [0.17, 18.94] |
| **Subtotal (95% CI)** | | **53** | | **47** | **100.0%** | **1.77 [0.17, 18.94]** |



Total events 2 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.47 (P = 0.64)

**7.7.5 Pharyngitis**

| | | | | | | |
|---|---|---|---|---|---|---|
| Findling 2006 | 4 | 133 | 0 | 46 | 30.4% | 3.16 [0.17, 57.53] |
| Lin 2014 | 2 | 36 | 2 | 78 | 69.6% | 2.17 [0.32, 14.78] |
| **Subtotal (95% CI)** | | **169** | | **124** | **100.0%** | **2.43 [0.49, 12.05]** |
| Total events | 6 | | 2 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.09 (P = 0.28)

**7.7.6 Pyrexia**

| | | | | | | |
|---|---|---|---|---|---|---|
| Coghill 2013 | 5 | 111 | 0 | 110 | 47.9% | 10.90 [0.61, 194.82] |
| Findling 2006 | 1 | 133 | 3 | 46 | 52.1% | 0.12 [0.01, 1.08] |
| **Subtotal (95% CI)** | | **244** | | **156** | **100.0%** | **1.02 [0.01, 87.72]** |
| Total events | 6 | | 3 | | | |

Heterogeneity: Tau² = 8.61; Chi² = 5.97, df = 1 (P = 0.01); I² = 83%
Test for overall effect: Z = 0.01 (P = 0.99)

**7.7.7 Rhinitis**

| | | | | | | |
|---|---|---|---|---|---|---|
| Wigal 2004 | 11 | 90 | 4 | 42 | 100.0% | 1.28 [0.43, 3.79] |
| **Subtotal (95% CI)** | | **90** | | **42** | **100.0%** | **1.28 [0.43, 3.79]** |
| Total events | 11 | | 4 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)

**7.7.8 Upper respiratory tract infection - not otherwise specified (NOS)**

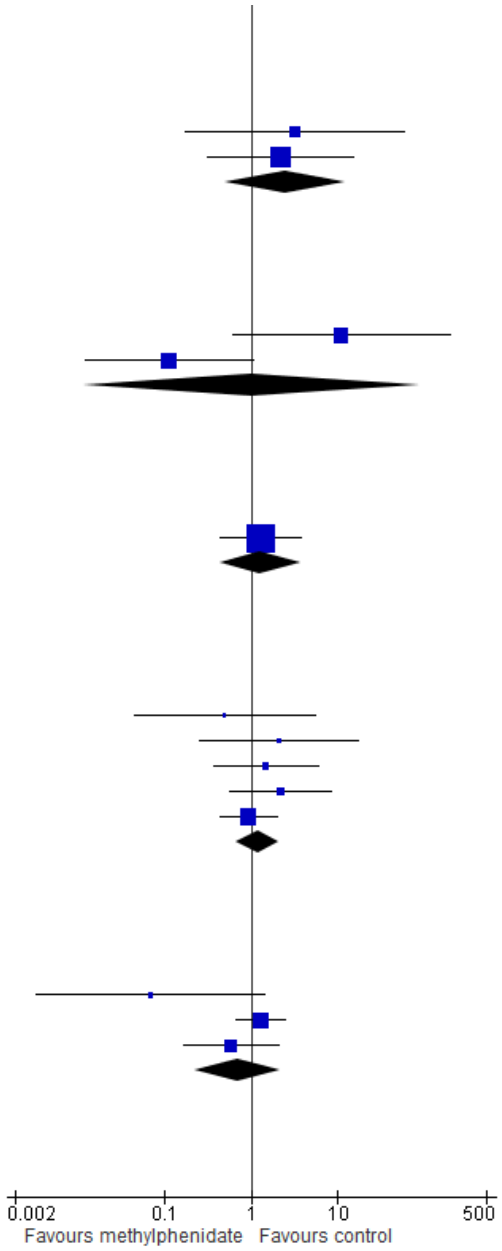
| | | | | | | |
|---|---|---|---|---|---|---|
| Coghill 2013 | 1 | 111 | 2 | 110 | 5.4% | 0.50 [0.05, 5.39] |
| Findling 2006 | 6 | 133 | 1 | 46 | 7.0% | 2.08 [0.26, 16.78] |
| Greenhill 2006 | 5 | 53 | 3 | 47 | 16.1% | 1.48 [0.37, 5.85] |
| Lin 2014 | 4 | 36 | 4 | 78 | 17.3% | 2.17 [0.57, 8.18] |
| Riggs 2011 | 12 | 151 | 13 | 152 | 54.1% | 0.93 [0.44, 1.97] |
| **Subtotal (95% CI)** | | **484** | | **433** | **100.0%** | **1.19 [0.68, 2.06]** |
| Total events | 28 | | 23 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 2.08, df = 4 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)

**7.7.9 Viral infection NOS**

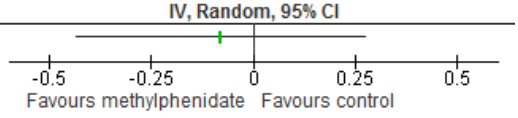
| | | | | | | |
|---|---|---|---|---|---|---|
| Findling 2006 | 0 | 133 | 2 | 46 | 11.4% | 0.07 [0.00, 1.43] |
| Riggs 2011 | 18 | 151 | 14 | 152 | 52.9% | 1.29 [0.67, 2.51] |
| Wigal 2004 | 5 | 90 | 4 | 42 | 35.6% | 0.58 [0.17, 2.06] |
| **Subtotal (95% CI)** | | **374** | | **240** | **100.0%** | **0.70 [0.23, 2.15]** |
| Total events | 23 | | 20 | | | |

Heterogeneity: Tau² = 0.51; Chi² = 4.26, df = 2 (P = 0.12); I² = 53%
Test for overall effect: Z = 0.63 (P = 0.53)




**7.8 Height**

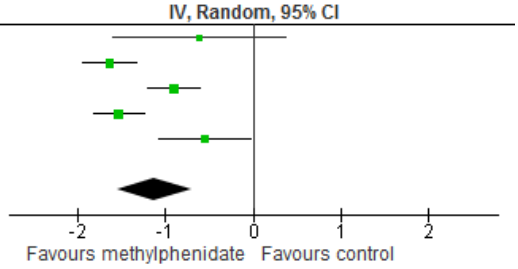
| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| Findling 2010 | 0.53 | 1.21 | 143 | 0.61 | 1.27 | 72 | -0.08 [-0.43, 0.27] |



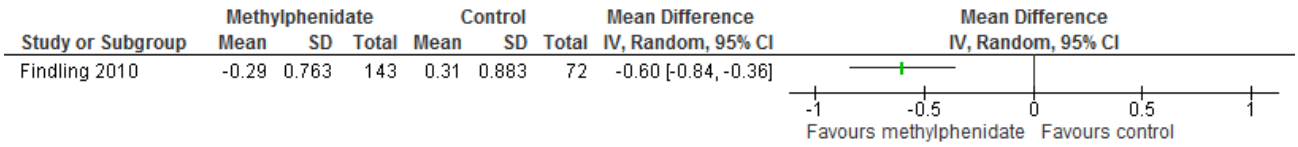

**7.9 Weight**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Carlson 2007 | -0.89 | 1.71 | 9 | -0.05 | 0.47 | 8 | 11.0% | -0.62 [-1.60, 0.36] |
| Coghill 2013 | -1.3 | 1.4 | 111 | 0.7 | 1 | 110 | 23.2% | -1.64 [-1.94, -1.33] |
| Findling 2010 | -1.9 | 3.87 | 143 | 1.77 | 4.385 | 72 | 23.4% | -0.90 [-1.20, -0.61] |
| Newcorn 2008 | -0.9 | 1.3 | 219 | 1.1 | 1.3 | 74 | 23.5% | -1.53 [-1.83, -1.24] |
| Palumbo 2008 | 0.3 | 2.3 | 29 | 1.4 | 1.6 | 30 | 18.9% | -0.55 [-1.07, -0.03] |
| **Total (95% CI)** | | | **511** | | | **294** | **100.0%** | **-1.12 [-1.55, -0.70]** |

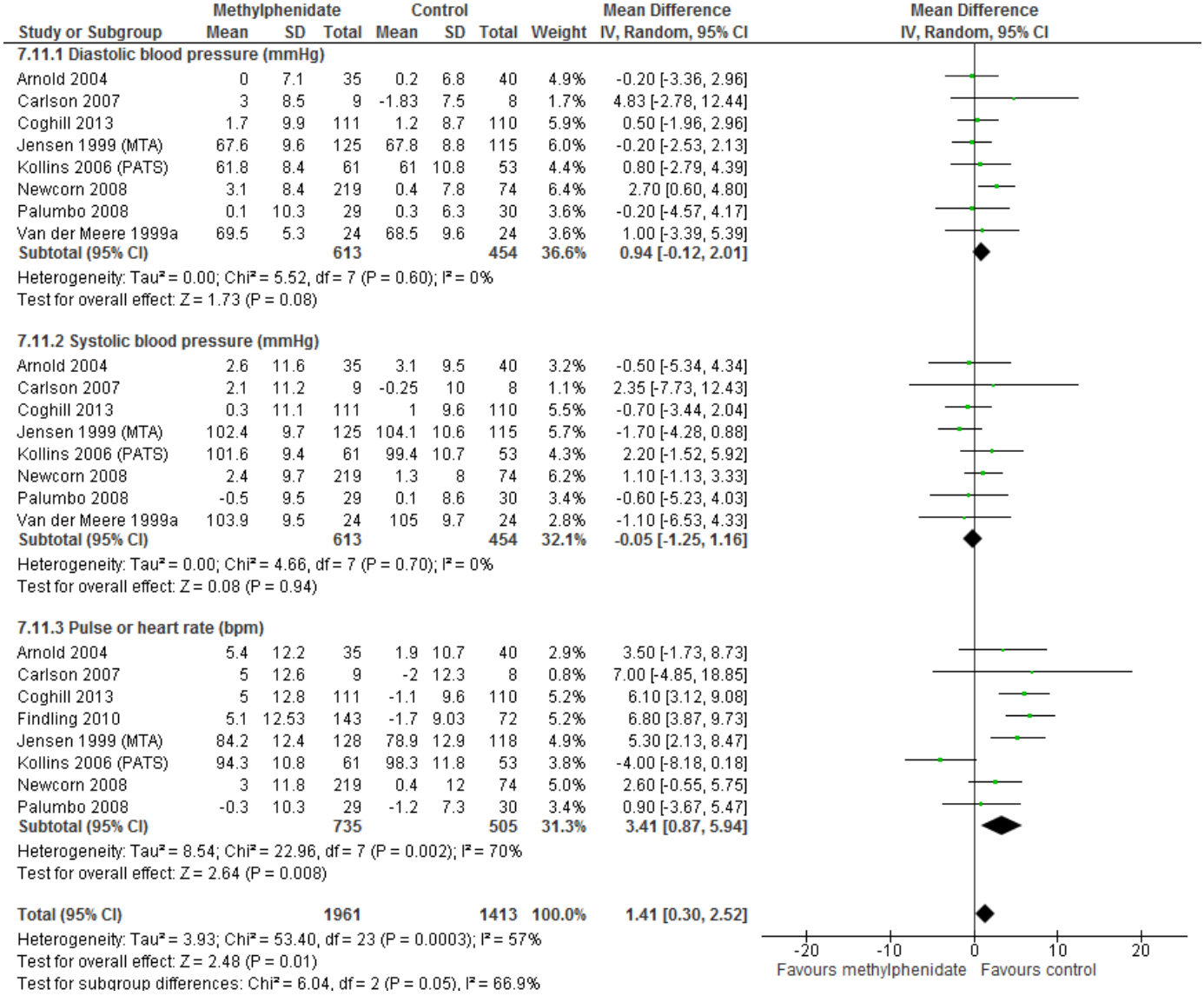
Heterogeneity: Tau² = 0.18; Chi² = 23.63, df = 4 (P < 0.0001); I² = 83%
Test for overall effect: Z = 5.15 (P < 0.00001)



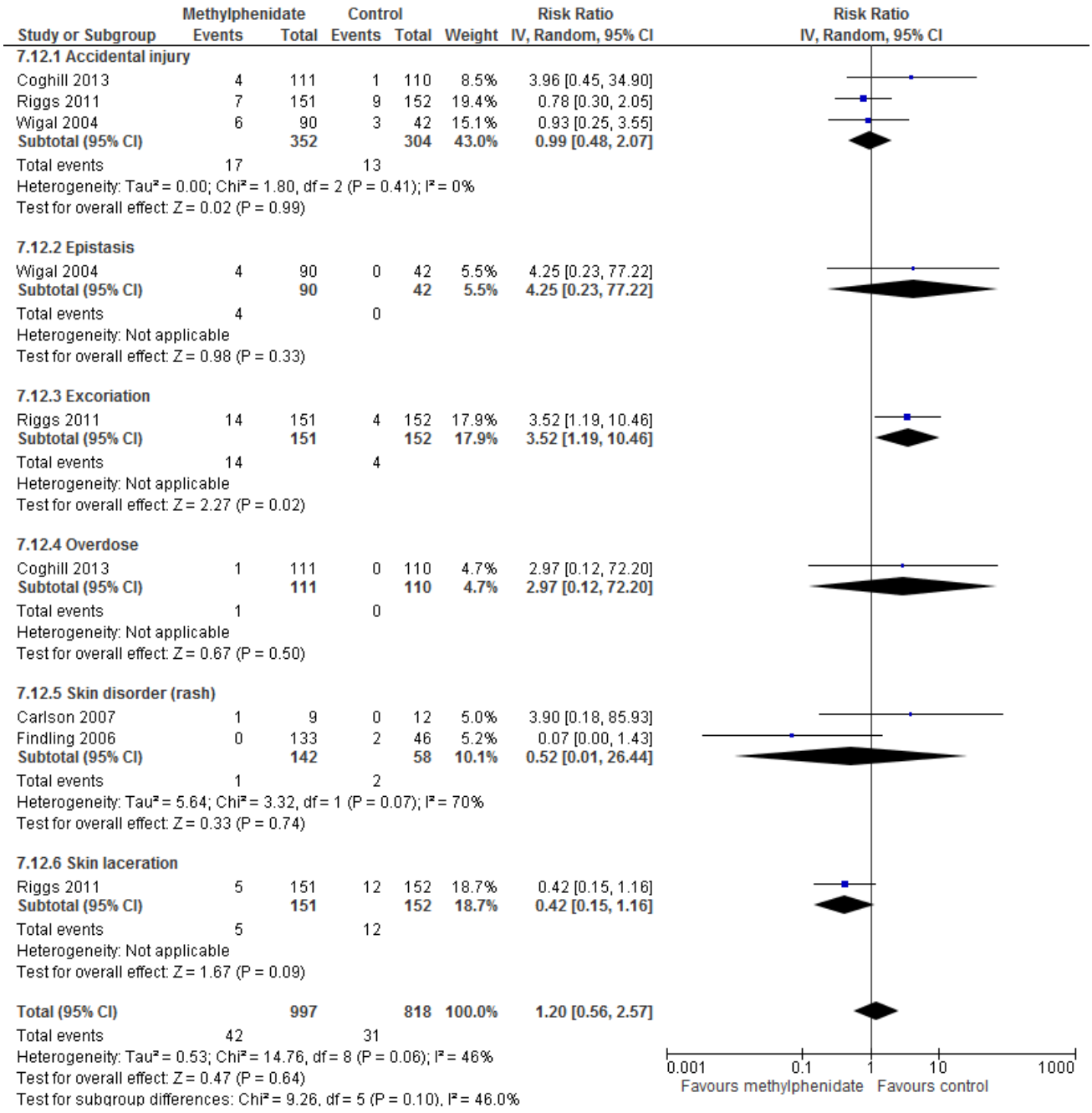
**7.10 BMI**




**7.11 Vital signs**



7.12 Other

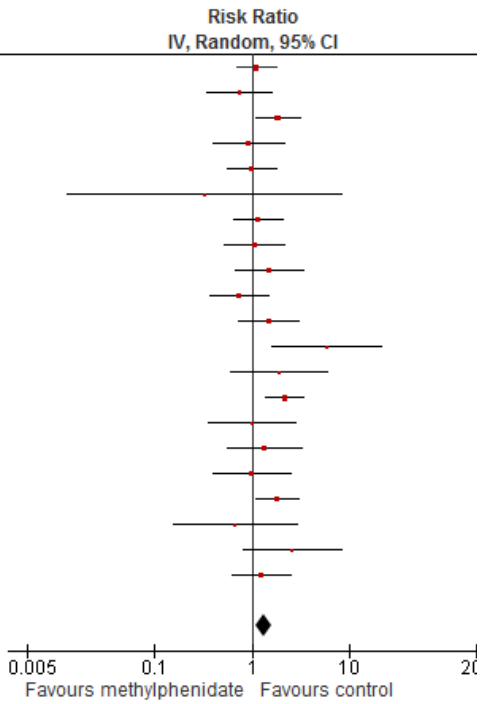



## 8 - Number of non-serious adverse events: cross-over trials (endpoint data)

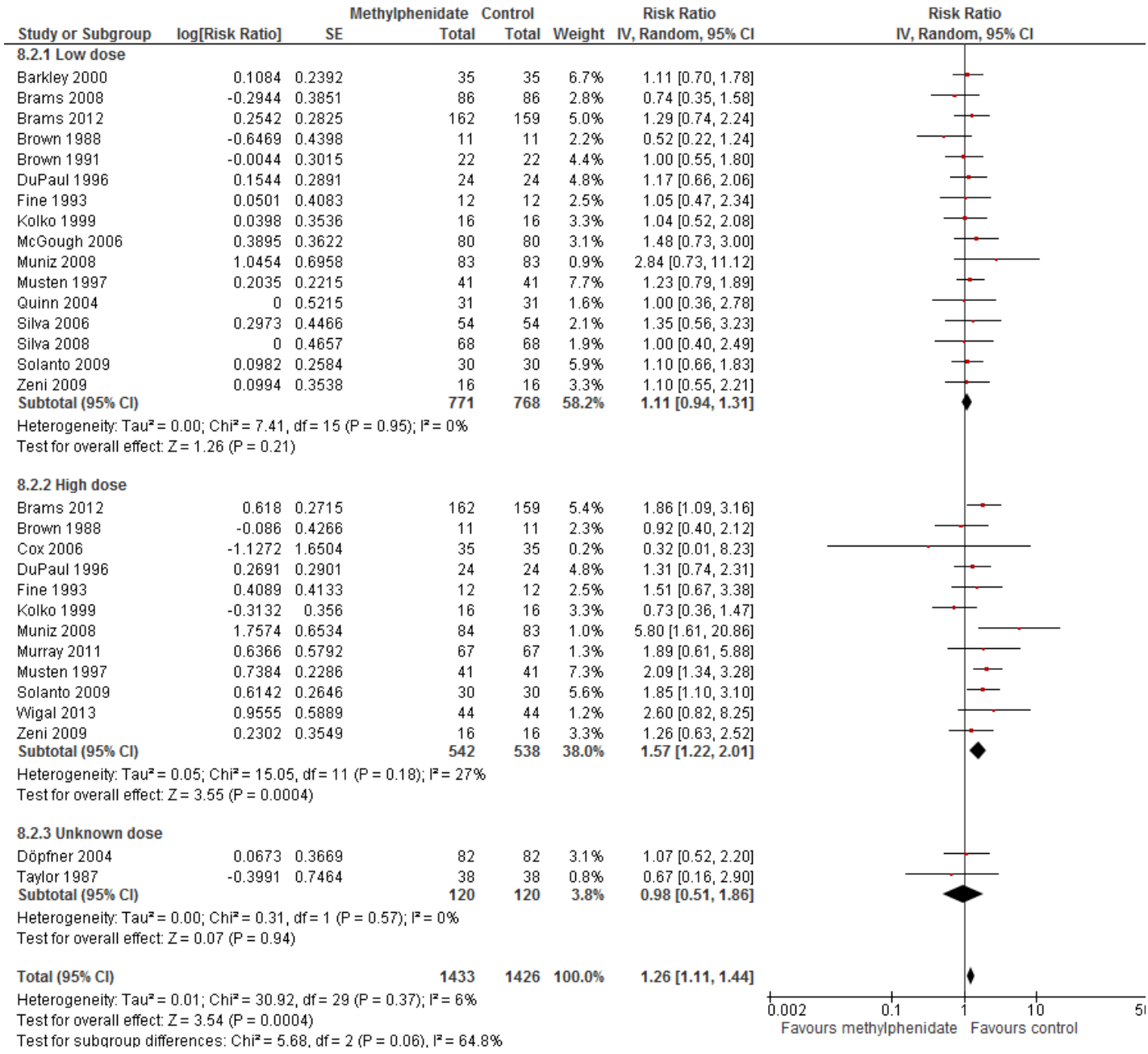
**8.1 Total number of non-serious adverse events**

| Study or Subgroup | log[Risk Ratio] | SE | Methylphenidate Total | Control Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Barkley 2000 | 0.1084 | 0.2392 | 35 | 35 | 9.4% | 1.11 [0.70, 1.78] |
| Brams 2008 | -0.2944 | 0.3851 | 86 | 86 | 4.6% | 0.74 [0.35, 1.58] |
| Brams 2012 | 0.6095 | 0.2714 | 162 | 159 | 7.9% | 1.84 [1.08, 3.13] |
| Brown 1988 | -0.086 | 0.4266 | 11 | 11 | 3.9% | 0.92 [0.40, 2.12] |
| Brown 1991 | -0.0044 | 0.3015 | 22 | 22 | 6.8% | 1.00 [0.55, 1.80] |
| Cox 2006 | -1.1272 | 1.6504 | 35 | 35 | 0.3% | 0.32 [0.01, 8.23] |
| DuPaul 1996 | 0.1544 | 0.2891 | 24 | 24 | 7.2% | 1.17 [0.66, 2.06] |
| Döpfner 2004 | 0.0673 | 0.3669 | 82 | 82 | 5.0% | 1.07 [0.52, 2.20] |
| Fine 1993 | 0.4089 | 0.4133 | 12 | 12 | 4.1% | 1.51 [0.67, 3.38] |
| Kolko 1999 | -0.3132 | 0.356 | 16 | 16 | 5.2% | 0.73 [0.36, 1.47] |
| McGough 2006 | 0.3895 | 0.3622 | 80 | 80 | 5.1% | 1.48 [0.73, 3.00] |
| Muniz 2008 | 1.7574 | 0.6534 | 84 | 83 | 1.8% | 5.80 [1.61, 20.86] |
| Murray 2011 | 0.6366 | 0.5792 | 67 | 67 | 2.2% | 1.89 [0.61, 5.88] |
| Musten 1997 | 0.779 | 0.2295 | 41 | 41 | 9.9% | 2.18 [1.39, 3.42] |
| Quinn 2004 | 0 | 0.5215 | 31 | 31 | 2.7% | 1.00 [0.36, 2.78] |
| Silva 2006 | 0.2973 | 0.4466 | 54 | 54 | 3.6% | 1.35 [0.56, 3.23] |
| Silva 2008 | 0 | 0.4657 | 68 | 68 | 3.3% | 1.00 [0.40, 2.49] |
| Solanto 2009 | 0.5932 | 0.2642 | 30 | 30 | 8.2% | 1.81 [1.08, 3.04] |
| Taylor 1987 | -0.3991 | 0.7464 | 38 | 38 | 1.4% | 0.67 [0.16, 2.90] |
| Wigal 2013 | 0.9555 | 0.5889 | 44 | 44 | 2.2% | 2.60 [0.82, 8.25] |
| Zeni 2009 | 0.2302 | 0.3549 | 16 | 16 | 5.3% | 1.26 [0.63, 2.52] |
| **Total (95% CI)** | | | **1038** | **1034** | **100.0%** | **1.33 [1.11, 1.58]** |

Heterogeneity: Tau² = 0.03; Chi² = 24.46, df = 20 (P = 0.22); I² = 18%
Test for overall effect: Z = 3.12 (P = 0.002)



8.2 Subgroup analysis: total number of non-serious adverse events according to dose



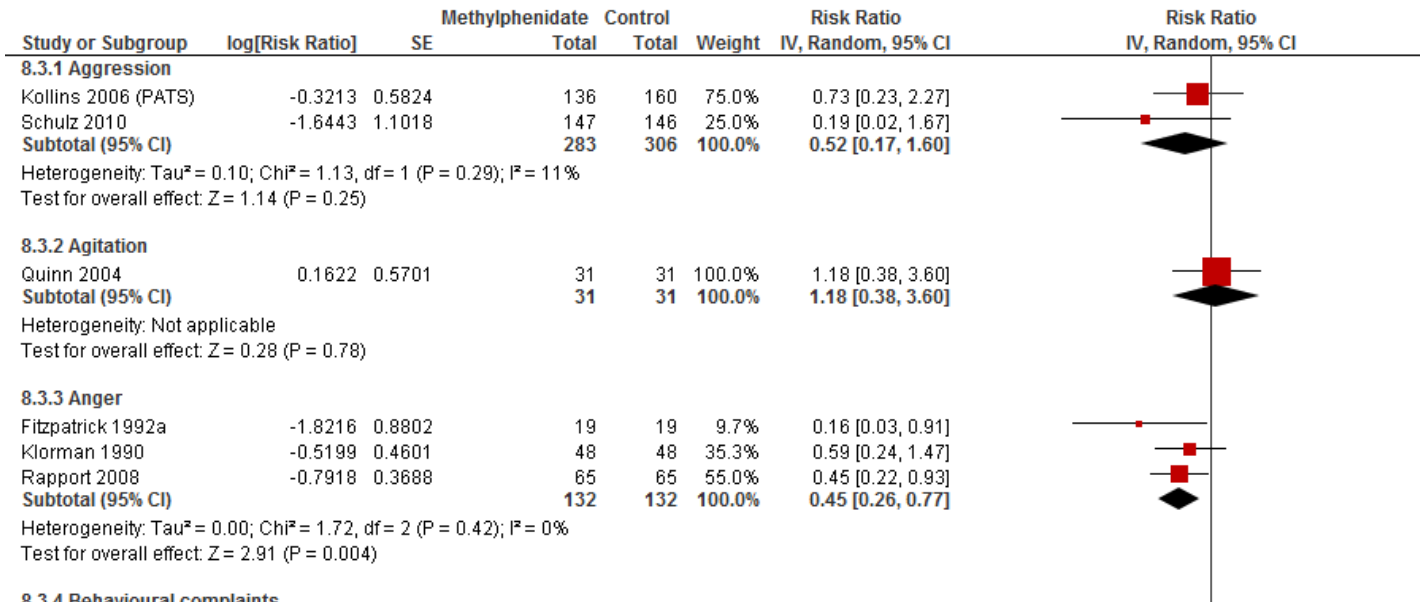
| Study or Subgroup | log[Risk Ratio] | SE | Methylphenidate Total | Control Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **8.2.1 Low dose** | | | | | | |
| Barkley 2000 | 0.1084 | 0.2392 | 35 | 35 | 6.7% | 1.11 [0.70, 1.78] |
| Brams 2008 | -0.2944 | 0.3851 | 86 | 86 | 2.8% | 0.74 [0.35, 1.58] |
| Brams 2012 | 0.2542 | 0.2825 | 162 | 159 | 5.0% | 1.29 [0.74, 2.24] |
| Brown 1988 | -0.6469 | 0.4398 | 11 | 11 | 2.2% | 0.52 [0.22, 1.24] |
| Brown 1991 | -0.0044 | 0.3015 | 22 | 22 | 4.4% | 1.00 [0.55, 1.80] |
| DuPaul 1996 | 0.1544 | 0.2891 | 24 | 24 | 4.8% | 1.17 [0.66, 2.06] |
| Fine 1993 | 0.0501 | 0.4083 | 12 | 12 | 2.5% | 1.05 [0.47, 2.34] |
| Kolko 1999 | 0.0398 | 0.3536 | 16 | 16 | 3.3% | 1.04 [0.52, 2.08] |
| McGough 2006 | 0.3895 | 0.3622 | 80 | 80 | 3.1% | 1.48 [0.73, 3.00] |
| Muniz 2008 | 1.0454 | 0.6958 | 83 | 83 | 0.9% | 2.84 [0.73, 11.12] |
| Musten 1997 | 0.2035 | 0.2215 | 41 | 41 | 7.7% | 1.23 [0.79, 1.89] |
| Quinn 2004 | 0 | 0.5215 | 31 | 31 | 1.6% | 1.00 [0.36, 2.78] |
| Silva 2006 | 0.2973 | 0.4466 | 54 | 54 | 2.1% | 1.35 [0.56, 3.23] |
| Silva 2008 | 0 | 0.4657 | 68 | 68 | 1.9% | 1.00 [0.40, 2.49] |
| Solanto 2009 | 0.0982 | 0.2584 | 30 | 30 | 5.9% | 1.10 [0.66, 1.83] |
| Zeni 2009 | 0.0994 | 0.3538 | 16 | 16 | 3.3% | 1.10 [0.55, 2.21] |
| **Subtotal (95% CI)** | | | **771** | **768** | **58.2%** | **1.11 [0.94, 1.31]** |
| Heterogeneity: Tau² = 0.00; Chi² = 7.41, df = 15 (P = 0.95); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.26 (P = 0.21) | | | | | | |
| **8.2.2 High dose** | | | | | | |
| Brams 2012 | 0.618 | 0.2715 | 162 | 159 | 5.4% | 1.86 [1.09, 3.16] |
| Brown 1988 | -0.086 | 0.4266 | 11 | 11 | 2.3% | 0.92 [0.40, 2.12] |
| Cox 2006 | -1.1272 | 1.6504 | 35 | 35 | 0.2% | 0.32 [0.01, 8.23] |
| DuPaul 1996 | 0.2691 | 0.2901 | 24 | 24 | 4.8% | 1.31 [0.74, 2.31] |
| Fine 1993 | 0.4089 | 0.4133 | 12 | 12 | 2.5% | 1.51 [0.67, 3.38] |
| Kolko 1999 | -0.3132 | 0.356 | 16 | 16 | 3.3% | 0.73 [0.36, 1.47] |
| Muniz 2008 | 1.7574 | 0.6534 | 84 | 83 | 1.0% | 5.80 [1.61, 20.86] |
| Murray 2011 | 0.6366 | 0.5792 | 67 | 67 | 1.3% | 1.89 [0.61, 5.88] |
| Musten 1997 | 0.7384 | 0.2286 | 41 | 41 | 7.3% | 2.09 [1.34, 3.28] |
| Solanto 2009 | 0.6142 | 0.2646 | 30 | 30 | 5.6% | 1.85 [1.10, 3.10] |
| Wigal 2013 | 0.9555 | 0.5889 | 44 | 44 | 1.2% | 2.60 [0.82, 8.25] |
| Zeni 2009 | 0.2302 | 0.3549 | 16 | 16 | 3.3% | 1.26 [0.63, 2.52] |
| **Subtotal (95% CI)** | | | **542** | **538** | **38.0%** | **1.57 [1.22, 2.01]** |
| Heterogeneity: Tau² = 0.05; Chi² = 15.05, df = 11 (P = 0.18); I² = 27% | | | | | | |
| Test for overall effect: Z = 3.55 (P = 0.0004) | | | | | | |
| **8.2.3 Unknown dose** | | | | | | |
| Döpfner 2004 | 0.0673 | 0.3669 | 82 | 82 | 3.1% | 1.07 [0.52, 2.20] |
| Taylor 1987 | -0.3991 | 0.7464 | 38 | 38 | 0.8% | 0.67 [0.16, 2.90] |
| **Subtotal (95% CI)** | | | **120** | **120** | **3.8%** | **0.98 [0.51, 1.86]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 1 (P = 0.57); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.07 (P = 0.94) | | | | | | |
| **Total (95% CI)** | | | **1433** | **1426** | **100.0%** | **1.26 [1.11, 1.44]** |
| Heterogeneity: Tau² = 0.01; Chi² = 30.92, df = 29 (P = 0.37); I² = 6% | | | | | | |
| Test for overall effect: Z = 3.54 (P = 0.0004) | | | | | | |
| Test for subgroup differences: Chi² = 5.68, df = 2 (P = 0.06), I² = 64.8% | | | | | | |

Risk Ratio IV, Random, 95% CI

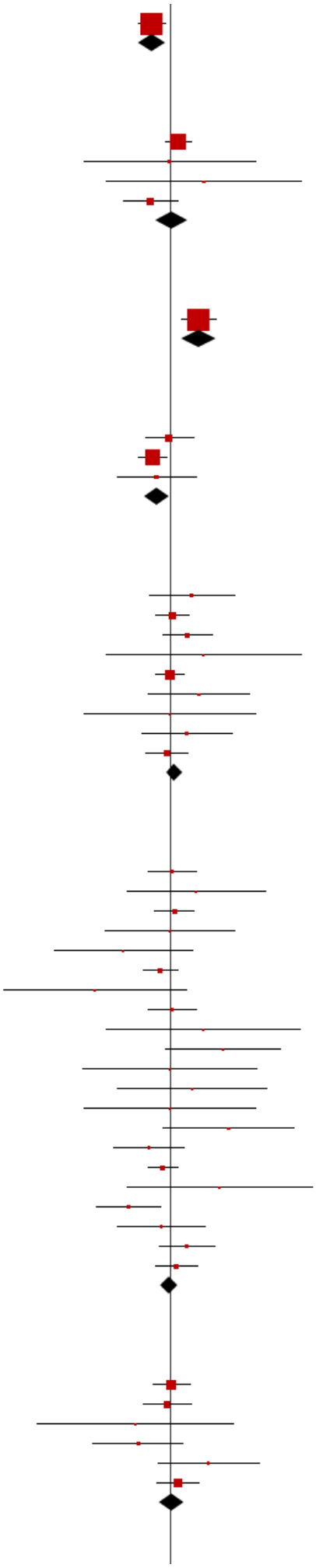
0.002 0.1 1 10 5

Favours methylphenidate Favours control

8.3 Nervous system



| Study or Subgroup | log[Risk Ratio] | SE | Methylphenidate Total | Control Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **8.3.1 Aggression** | | | | | | |
| Kollins 2006 (PATS) | -0.3213 | 0.5824 | 136 | 160 | 75.0% | 0.73 [0.23, 2.27] |
| Schulz 2010 | -1.6443 | 1.1018 | 147 | 146 | 25.0% | 0.19 [0.02, 1.67] |
| **Subtotal (95% CI)** | | | **283** | **306** | **100.0%** | **0.52 [0.17, 1.60]** |
| Heterogeneity: Tau² = 0.10; Chi² = 1.13, df = 1 (P = 0.29); I² = 11% | | | | | | |
| Test for overall effect: Z = 1.14 (P = 0.25) | | | | | | |
| **8.3.2 Agitation** | | | | | | |
| Quinn 2004 | 0.1622 | 0.5701 | 31 | 31 | 100.0% | 1.18 [0.38, 3.60] |
| **Subtotal (95% CI)** | | | **31** | **31** | **100.0%** | **1.18 [0.38, 3.60]** |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.28 (P = 0.78) | | | | | | |
| **8.3.3 Anger** | | | | | | |
| Fitzpatrick 1992a | -1.8216 | 0.8802 | 19 | 19 | 9.7% | 0.16 [0.03, 0.91] |
| Klorman 1990 | -0.5199 | 0.4601 | 48 | 48 | 35.3% | 0.59 [0.24, 1.47] |
| Rapport 2008 | -0.7918 | 0.3688 | 65 | 65 | 55.0% | 0.45 [0.22, 0.93] |
| **Subtotal (95% CI)** | | | **132** | **132** | **100.0%** | **0.45 [0.26, 0.77]** |
| Heterogeneity: Tau² = 0.00; Chi² = 1.72, df = 2 (P = 0.42); I² = 0% | | | | | | |
| Test for overall effect: Z = 2.91 (P = 0.004) | | | | | | |
| 8.3.4 Behavioural complaints | | | | | | |



| | | | | | | |
|---|---|---|---|---|---|---|
| Gorman 2006 | -0.5936 | 0.2259 | 41 | 41 | 100.0% | 0.55 [0.35, 0.86] |
| **Subtotal (95% CI)** | | | **41** | **41** | **100.0%** | **0.55 [0.35, 0.86]** |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 2.63 (P = 0.009) | | | | | | |
| **8.3.5 Buccal or lingual movements** | | | | | | |
| Borcherding 1990 | 0.2804 | 0.2119 | 45 | 45 | 67.9% | 1.32 [0.87, 2.01] |
| Pelham 1999 | 0 | 1.4434 | 25 | 25 | 3.4% | 1.00 [0.06, 16.93] |
| Pelham 2005 | 1.1264 | 1.6499 | 36 | 36 | 2.6% | 3.08 [0.12, 78.27] |
| Smith 1998 | -0.6295 | 0.4635 | 45 | 45 | 26.1% | 0.53 [0.21, 1.32] |
| **Subtotal (95% CI)** | | | **151** | **151** | **100.0%** | **1.06 [0.62, 1.79]** |
| Heterogeneity: Tau² = 0.06; Chi² = 3.56, df = 3 (P = 0.31); I² = 16% | | | | | | |
| Test for overall effect: Z = 0.20 (P = 0.84) | | | | | | |
| **8.3.6 Compulsive acts** | | | | | | |
| Borcherding 1990 | 0.943 | 0.293 | 45 | 45 | 100.0% | 2.57 [1.45, 4.56] |
| **Subtotal (95% CI)** | | | **45** | **45** | **100.0%** | **2.57 [1.45, 4.56]** |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 3.22 (P = 0.001) | | | | | | |
| **8.3.7 Daydreaming** | | | | | | |
| Fine 1993 | -0.0145 | 0.4083 | 12 | 12 | 24.5% | 0.99 [0.44, 2.19] |
| Ramtvedt 2013 | -0.5681 | 0.2477 | 34 | 34 | 66.5% | 0.57 [0.35, 0.92] |
| Rapport 2008 | -0.4388 | 0.6708 | 65 | 65 | 9.1% | 0.64 [0.17, 2.40] |
| **Subtotal (95% CI)** | | | **111** | **111** | **100.0%** | **0.66 [0.44, 0.98]** |
| Heterogeneity: Tau² = 0.00; Chi² = 1.34, df = 2 (P = 0.51); I² = 0% | | | | | | |
| Test for overall effect: Z = 2.08 (P = 0.04) | | | | | | |
| **8.3.8 Dizziness** | | | | | | |
| Barkley 1989 | 0.7319 | 0.7251 | 82 | 82 | 3.9% | 2.08 [0.50, 8.61] |
| DuPaul 1996 | 0.0787 | 0.2888 | 24 | 24 | 24.7% | 1.08 [0.61, 1.91] |
| Fine 1993 | 0.5948 | 0.4189 | 12 | 12 | 11.7% | 1.81 [0.80, 4.12] |
| Pelham 2001a | 1.1133 | 1.642 | 68 | 68 | 0.8% | 3.04 [0.12, 76.06] |
| Ramtvedt 2013 | 0 | 0.2425 | 34 | 34 | 35.0% | 1.00 [0.62, 1.61] |
| Rapport 2008 | 0.9651 | 0.8559 | 65 | 65 | 2.8% | 2.63 [0.49, 14.05] |
| Stein 1996 | 0 | 1.4434 | 25 | 25 | 1.0% | 1.00 [0.06, 16.93] |
| Stein 2003 | 0.5573 | 0.7615 | 47 | 47 | 3.6% | 1.75 [0.39, 7.77] |
| Zeni 2009 | -0.082 | 0.3537 | 16 | 16 | 16.5% | 0.92 [0.46, 1.84] |
| **Subtotal (95% CI)** | | | **373** | **373** | **100.0%** | **1.17 [0.89, 1.55]** |
| Heterogeneity: Tau² = 0.00; Chi² = 4.19, df = 8 (P = 0.84); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.11 (P = 0.27) | | | | | | |
| **8.3.9 Drowsiness: dull, tired, listless or sleepy** | | | | | | |
| Barkley 1989 | 0.0796 | 0.3991 | 82 | 82 | 8.7% | 1.08 [0.50, 2.37] |
| Buitelaar 1995 | 0.8675 | 1.1609 | 26 | 11 | 1.4% | 2.38 [0.24, 23.17] |
| Bukstein 1998 | 0.1588 | 0.3339 | 18 | 18 | 10.9% | 1.17 [0.61, 2.26] |
| Carlson 1995 | 0 | 1.0954 | 12 | 12 | 1.6% | 1.00 [0.12, 8.56] |
| Chronis 2003 | -1.5488 | 1.1657 | 21 | 21 | 1.4% | 0.21 [0.02, 2.09] |
| DuPaul 1996 | -0.324 | 0.2907 | 24 | 24 | 12.7% | 0.72 [0.41, 1.28] |
| Findling 2007 | -2.4749 | 1.5371 | 13 | 13 | 0.8% | 0.08 [0.00, 1.71] |
| Fine 1993 | 0.0719 | 0.4084 | 12 | 12 | 8.4% | 1.07 [0.48, 2.39] |
| Muniz 2008 | 1.0986 | 1.6403 | 84 | 83 | 0.7% | 3.00 [0.12, 74.70] |
| Musten 1997 | 1.76 | 0.9632 | 41 | 41 | 2.0% | 5.81 [0.88, 38.39] |
| Overtoom 2003 | 0 | 1.4606 | 16 | 16 | 0.9% | 1.00 [0.06, 17.51] |
| Pearson 2013 | 0.7376 | 1.2605 | 24 | 24 | 1.2% | 2.09 [0.18, 24.73] |
| Pelham 1990a | 0 | 1.4475 | 22 | 22 | 0.9% | 1.00 [0.06, 17.07] |
| Pelham 2005 | 1.9459 | 1.1084 | 36 | 36 | 1.6% | 7.00 [0.80, 61.46] |
| Quinn 2004 | -0.6852 | 0.5952 | 31 | 31 | 4.8% | 0.50 [0.16, 1.62] |
| Ramtvedt 2013 | -0.2237 | 0.2433 | 34 | 34 | 15.0% | 0.80 [0.50, 1.29] |
| Silva 2006 | 1.6468 | 1.5612 | 54 | 54 | 0.8% | 5.19 [0.24, 110.69] |
| Smith 1998 | -1.3728 | 0.5356 | 45 | 45 | 5.6% | 0.25 [0.09, 0.72] |
| Stein 1996 | -0.2719 | 0.74 | 25 | 25 | 3.3% | 0.76 [0.18, 3.25] |
| Stein 2003 | 0.5736 | 0.4612 | 47 | 47 | 7.1% | 1.77 [0.72, 4.38] |
| Zeni 2009 | 0.222 | 0.3548 | 16 | 16 | 10.1% | 1.25 [0.62, 2.50] |
| **Subtotal (95% CI)** | | | **683** | **667** | **100.0%** | **0.97 [0.73, 1.28]** |
| Heterogeneity: Tau² = 0.08; Chi² = 25.33, df = 20 (P = 0.19); I² = 21% | | | | | | |
| Test for overall effect: Z = 0.23 (P = 0.81) | | | | | | |
| **8.3.10 Euphoria** | | | | | | |
| Barkley 1989 | 0.05 | 0.3164 | 82 | 82 | 35.6% | 1.05 [0.57, 1.95] |
| Fine 1993 | -0.0847 | 0.4085 | 12 | 12 | 22.2% | 0.92 [0.41, 2.05] |
| Pearson 2013 | -1.1403 | 1.6583 | 24 | 24 | 1.4% | 0.32 [0.01, 8.25] |
| Stein 1996 | -1.048 | 0.7597 | 25 | 25 | 6.7% | 0.35 [0.08, 1.55] |
| Stein 2011 | 1.2763 | 0.8472 | 42 | 45 | 5.4% | 3.58 [0.68, 18.86] |
| Zeni 2009 | 0.2756 | 0.3555 | 16 | 16 | 28.7% | 1.32 [0.66, 2.64] |
| **Subtotal (95% CI)** | | | **201** | **204** | **100.0%** | **1.06 [0.72, 1.57]** |
| Heterogeneity: Tau² = 0.01; Chi² = 5.21, df = 5 (P = 0.39); I² = 4% | | | | | | |
| Test for overall effect: Z = 0.31 (P = 0.76) | | | | | | |

### 8.3.11 Headache

| | | | | | | |
|---|---|---|---|---|---|---|
| Barkley 1989 | 0.7521 | 0.4461 | 82 | 82 | 4.4% | 2.12 [0.88, 5.09] |
| Brams 2008 | 0.4174 | 0.9259 | 86 | 86 | 1.0% | 1.52 [0.25, 9.32] |
| Brams 2012 | 0.8473 | 0.6993 | 163 | 159 | 1.8% | 2.33 [0.59, 9.19] |
| Buitelaar 1995 | -0.4543 | 0.8402 | 26 | 11 | 1.3% | 0.63 [0.12, 3.30] |
| Bukstein 1998 | -0.0726 | 0.312 | 18 | 18 | 9.1% | 0.93 [0.50, 1.71] |
| Carlson 1995 | -0.7885 | 1.3003 | 12 | 12 | 0.5% | 0.45 [0.04, 5.81] |
| Chronis 2003 | -2.4031 | 1.5251 | 21 | 21 | 0.4% | 0.09 [0.00, 1.80] |
| DuPaul 1996 | -0.10884 | 0.6628 | 24 | 24 | 2.0% | 0.90 [0.24, 3.29] |
| Fine 1993 | 0.2612 | 0.4103 | 12 | 12 | 5.2% | 1.30 [0.58, 2.90] |
| Fitzpatrick 1992a | 0 | 1.0572 | 19 | 19 | 0.8% | 1.00 [0.13, 7.94] |
| Klorman 1990 | 0.7621 | 0.7389 | 48 | 48 | 1.6% | 2.14 [0.50, 9.12] |
| McBride 1988a | 0.4274 | 0.9366 | 48 | 48 | 1.0% | 1.53 [0.24, 9.61] |
| McGough 2006 | 0 | 0.8323 | 80 | 80 | 1.3% | 1.00 [0.20, 5.11] |
| Muniz 2008 | 2.6267 | 1.476 | 84 | 83 | 0.4% | 13.83 [0.77, 249.54] |
| Murray 2011 | 0.7244 | 0.8839 | 67 | 67 | 1.1% | 2.06 [0.36, 11.67] |
| Musten 1997 | 0.4374 | 0.2236 | 41 | 41 | 17.7% | 1.55 [1.00, 2.40] |
| Pearson 2013 | 0.7885 | 0.9195 | 24 | 24 | 1.0% | 2.20 [0.36, 13.34] |
| Pelham 1990a | -1.7025 | 1.579 | 22 | 22 | 0.4% | 0.18 [0.01, 4.02] |
| Pelham 1999 | 1.5198 | 1.1573 | 25 | 25 | 0.7% | 4.57 [0.47, 44.17] |
| Pelham 2001a | -0.4665 | 0.4361 | 68 | 68 | 4.6% | 0.63 [0.27, 1.47] |
| Pelham 2005 | 0.5733 | 0.7719 | 36 | 36 | 1.5% | 1.77 [0.39, 8.05] |
| Quinn 2004 | -1.675 | 1.5702 | 31 | 31 | 0.4% | 0.19 [0.01, 4.07] |
| Ramtvedt 2013 | 0.1156 | 0.2428 | 34 | 34 | 15.0% | 1.12 [0.70, 1.81] |
| Rapport 2008 | 0.1712 | 0.5863 | 65 | 65 | 2.6% | 1.19 [0.38, 3.74] |
| Schachar 2008 | 0 | 1.4552 | 18 | 18 | 0.4% | 1.00 [0.06, 17.32] |
| Schulz 2010 | 0.3436 | 0.5976 | 147 | 146 | 2.5% | 1.41 [0.44, 4.55] |
| Silva 2005a | 0.6931 | 1.2403 | 54 | 53 | 0.6% | 2.00 [0.18, 22.74] |
| Silva 2006 | -1.1371 | 1.1712 | 54 | 54 | 0.6% | 0.32 [0.03, 3.18] |
| Silva 2008 | 0 | 1.4247 | 68 | 68 | 0.4% | 1.00 [0.06, 16.32] |
| Smith 1998 | -0.2076 | 0.646 | 45 | 45 | 2.1% | 0.81 [0.23, 2.88] |
| Stein 1996 | 0.9045 | 0.6939 | 25 | 25 | 1.8% | 2.47 [0.63, 9.63] |
| Stein 2003 | 0.0934 | 0.4323 | 47 | 47 | 4.7% | 1.10 [0.47, 2.56] |
| Stein 2011 | 1.1906 | 1.647 | 42 | 45 | 0.3% | 3.29 [0.13, 82.99] |
| Swanson 2004b | 0.1712 | 0.5665 | 181 | 183 | 2.8% | 1.19 [0.39, 3.60] |
| Wigal 2014 | 1.9904 | 1.4822 | 21 | 22 | 0.4% | 7.32 [0.40, 133.68] |
| Wilens 2010 | 1.7579 | 1.1289 | 30 | 30 | 0.7% | 5.80 [0.63, 53.01] |
| Zeni 2009 | -0.393 | 0.3574 | 16 | 16 | 6.9% | 0.68 [0.34, 1.36] |
| **Subtotal (95% CI)** | | | **1884** | **1868** | **100.0%** | **1.21 [1.01, 1.45]** |

Heterogeneity: Tau² = 0.00; Chi² = 29.25, df = 36 (P = 0.78); I² = 0%
Test for overall effect: Z = 2.02 (P = 0.04)

### 8.3.12 Insomnia or sleep problems

| | | | | | | |
|---|---|---|---|---|---|---|
| Barkley 1989 | 1.1626 | 0.3272 | 82 | 82 | 5.8% | 3.20 [1.68, 6.07] |
| Brams 2012 | 1.9397 | 1.516 | 163 | 159 | 0.8% | 6.96 [0.36, 135.78] |
| Buitelaar 1995 | 0.5108 | 0.7879 | 26 | 11 | 2.3% | 1.67 [0.36, 7.81] |
| Castellanos 1997 | 0.7419 | 1.264 | 22 | 22 | 1.0% | 2.10 [0.18, 25.01] |
| Chronis 2003 | -0.2838 | 0.7559 | 21 | 21 | 2.4% | 0.75 [0.17, 3.31] |
| Corkum 2008 | 1.0814 | 0.3326 | 21 | 21 | 5.8% | 2.95 [1.54, 5.66] |
| DuPaul 1996 | 0.3083 | 0.2905 | 24 | 24 | 6.3% | 1.36 [0.77, 2.41] |
| Findling 2007 | 1.1575 | 0.9286 | 16 | 16 | 1.8% | 3.18 [0.52, 19.64] |
| Fine 1993 | 0.346 | 0.4119 | 12 | 12 | 4.9% | 1.41 [0.63, 3.17] |
| Fitzpatrick 1992a | 1.3555 | 0.7821 | 19 | 19 | 2.3% | 3.88 [0.84, 17.96] |
| Klorman 1990 | 0.1582 | 0.5632 | 48 | 48 | 3.5% | 1.17 [0.39, 3.53] |
| Kollins 2006 (PATS) | 0.1782 | 0.4108 | 136 | 160 | 4.9% | 1.20 [0.53, 2.67] |
| Manos 1999 | 0.8952 | 0.5001 | 177 | 177 | 4.0% | 2.45 [0.92, 6.52] |
| Muniz 2008 | 1.0986 | 1.6403 | 84 | 83 | 0.7% | 3.00 [0.12, 74.70] |
| Musten 1997 | -0.7228 | 0.2283 | 41 | 41 | 7.0% | 0.49 [0.31, 0.76] |
| Pearson 2013 | 1.335 | 0.6475 | 24 | 24 | 3.0% | 3.80 [1.07, 13.52] |
| Pelham 1990a | 1.5404 | 1.4475 | 22 | 22 | 0.8% | 4.67 [0.27, 79.63] |
| Pelham 1999 | 0.8398 | 0.7734 | 25 | 25 | 2.3% | 2.32 [0.51, 10.54] |
| Pelham 2001a | -0.3687 | 0.6125 | 68 | 68 | 3.2% | 0.69 [0.21, 2.30] |
| Pelham 2005 | 0.9765 | 0.7355 | 36 | 36 | 2.5% | 2.66 [0.63, 11.22] |
| Ramtvedt 2013 | 0.2796 | 0.2438 | 34 | 34 | 6.8% | 1.32 [0.82, 2.13] |
| Rapport 2008 | -0.3704 | 0.6138 | 65 | 65 | 3.2% | 0.69 [0.21, 2.30] |
| Sharp 1999 | 0.7902 | 0.4528 | 48 | 48 | 4.5% | 2.20 [0.91, 5.35] |
| Silva 2006 | 1.6468 | 1.5612 | 54 | 54 | 0.7% | 5.19 [0.24, 110.69] |
| Stein 1996 | 0.4855 | 0.5718 | 25 | 25 | 3.5% | 1.62 [0.53, 4.98] |
| Stein 2003 | 0.7816 | 0.4222 | 47 | 47 | 4.8% | 2.18 [0.96, 5.00] |
| Stein 2011 | 0.5031 | 0.9393 | 42 | 45 | 1.7% | 1.65 [0.26, 10.42] |
| Swanson 2004b | -0.6988 | 0.715 | 181 | 183 | 2.6% | 0.50 [0.12, 2.02] |
| Wigal 2014 | -1.0542 | 1.6055 | 21 | 22 | 0.7% | 0.35 [0.01, 8.11] |
| Wilens 2010 | 3.1374 | 1.4815 | 30 | 30 | 0.8% | 23.04 [1.26, 420.35] |
| Zeni 2009 | -0.0382 | 0.3536 | 16 | 16 | 5.5% | 0.96 [0.48, 1.92] |
| **Subtotal (95% CI)** | | | **1630** | **1640** | **100.0%** | **1.57 [1.20, 2.06]** |

Heterogeneity: Tau² = 0.22; Chi² = 56.48, df = 30 (P = 0.002); I² = 47%
Test for overall effect: Z = 3.27 (P = 0.001)

### 8.3.13 Irritability

| | | | | | | |
|---|---|---|---|---|---|---|
| Barkley 1989 | -0.2853 | 0.3386 | 82 | 82 | 6.7% | 0.75 [0.39, 1.46] |
| Buitelaar 1995 | 0.1699 | 0.7993 | 26 | 11 | 3.0% | 1.19 [0.25, 5.68] |
| Bukstein 1998 | 0.1478 | 0.3338 | 18 | 18 | 6.8% | 1.16 [0.60, 2.23] |
| Chronis 2003 | -1.0986 | 0.7766 | 21 | 21 | 3.1% | 0.33 [0.07, 1.53] |
| DuPaul 1996 | 0.1088 | 1.4634 | 24 | 24 | 1.1% | 1.11 [0.06, 19.63] |
| Findling 2007 | -0.9555 | 0.8228 | 16 | 16 | 2.9% | 0.38 [0.08, 1.93] |
| Fine 1993 | 0.1065 | 0.4086 | 12 | 12 | 6.0% | 1.11 [0.50, 2.48] |
| Kollins 2006 (PATS) | -0.0409 | 0.4654 | 136 | 160 | 5.4% | 0.96 [0.39, 2.39] |
| Manos 1999 | -0.4727 | 0.2723 | 177 | 177 | 7.5% | 0.62 [0.37, 1.06] |
| Musten 1997 | 0.0646 | 0.2209 | 41 | 41 | 8.0% | 1.07 [0.69, 1.64] |
| Pearson 2013 | -0.5261 | 0.5961 | 24 | 24 | 4.3% | 0.59 [0.18, 1.90] |
| Pelham 1990a | -1.0788 | 0.8993 | 22 | 22 | 2.5% | 0.34 [0.06, 1.98] |
| Pelham 1999 | -0.9045 | 0.6939 | 25 | 25 | 3.6% | 0.40 [0.10, 1.58] |
| Pelham 2005 | 1.7308 | 1.1229 | 36 | 36 | 1.8% | 5.65 [0.62, 50.99] |
| Ramtvedt 2013 | -0.2417 | 0.2435 | 34 | 34 | 7.8% | 0.79 [0.49, 1.27] |
| Silva 2006 | -2.0025 | 1.5243 | 54 | 54 | 1.1% | 0.13 [0.01, 2.68] |
| Smith 1998 | -1.7518 | 0.4723 | 45 | 45 | 5.3% | 0.17 [0.07, 0.44] |
| Stein 1996 | 2.1401 | 0.6587 | 25 | 25 | 3.8% | 8.50 [2.34, 30.91] |
| Stein 2003 | 0.6613 | 0.4397 | 47 | 47 | 5.7% | 1.94 [0.82, 4.59] |
| Swanson 2004b | -0.9219 | 0.8433 | 181 | 183 | 2.8% | 0.40 [0.08, 2.08] |
| Wigal 2014 | -1.0542 | 1.6055 | 21 | 22 | 1.0% | 0.35 [0.01, 8.11] |
| Wilens 2010 | 1.7579 | 0.6928 | 30 | 30 | 3.6% | 5.80 [1.49, 22.55] |
| Zeni 2009 | 0.6467 | 0.3639 | 16 | 16 | 6.5% | 1.91 [0.94, 3.90] |
| **Subtotal (95% CI)** | | | **1113** | **1125** | **100.0%** | **0.92 [0.66, 1.27]** |

Heterogeneity: Tau² = 0.30; Chi² = 53.48, df = 22 (P = 0.0002); I² = 59%
Test for overall effect: Z = 0.52 (P = 0.60)

### 8.3.14 Nightmares

| | | | | | | |
|---|---|---|---|---|---|---|
| Barkley 1989 | 0.0759 | 0.3897 | 82 | 82 | 11.8% | 1.08 [0.50, 2.32] |
| Buitelaar 1995 | -0.1823 | 1.2813 | 26 | 11 | 2.1% | 0.83 [0.07, 10.27] |
| DuPaul 1996 | 0.3165 | 0.2906 | 24 | 24 | 14.9% | 1.37 [0.78, 2.43] |
| Fine 1993 | 0.1168 | 0.4087 | 12 | 12 | 11.3% | 1.12 [0.50, 2.50] |
| Musten 1997 | 0.6716 | 0.2273 | 41 | 41 | 17.1% | 1.96 [1.25, 3.06] |
| Ramtvedt 2013 | -0.1315 | 0.2428 | 34 | 34 | 16.6% | 0.88 [0.54, 1.41] |
| Stein 1996 | -1.867 | 0.8468 | 25 | 25 | 4.3% | 0.15 [0.03, 0.81] |
| Stein 2003 | -0.4346 | 0.543 | 47 | 47 | 8.2% | 0.65 [0.22, 1.88] |
| Stein 2011 | 1.1906 | 1.647 | 42 | 45 | 1.3% | 3.29 [0.13, 82.99] |
| Zeni 2009 | -0.7008 | 0.3657 | 16 | 16 | 12.5% | 0.50 [0.24, 1.02] |
| **Subtotal (95% CI)** | | | **349** | **337** | **100.0%** | **0.97 [0.66, 1.42]** |

Heterogeneity: Tau² = 0.17; Chi² = 19.43, df = 9 (P = 0.02); I² = 54%
Test for overall effect: Z = 0.15 (P = 0.88)

### 8.3.15 Overly meticulous

| | | | | | | |
|---|---|---|---|---|---|---|
| Sharp 1999 | 3.7079 | 1.4555 | 48 | 48 | 100.0% | 40.77 [2.35, 706.72] |
| **Subtotal (95% CI)** | | | **48** | **48** | **100.0%** | **40.77 [2.35, 706.72]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 2.55 (P = 0.01)

### 8.3.16 Obsessive thinking

| | | | | | | |
|---|---|---|---|---|---|---|
| Borcherding 1990 | 0.8547 | 0.2207 | 45 | 45 | 100.0% | 2.35 [1.53, 3.62] |
| **Subtotal (95% CI)** | | | **45** | **45** | **100.0%** | **2.35 [1.53, 3.62]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 3.87 (P = 0.0001)

### 8.3.17 Picking at skin or fingers, nail biting, lip or cheek chewing

| | | | | | | |
|---|---|---|---|---|---|---|
| Barkley 1989 | 0.3861 | 0.3607 | 82 | 82 | 10.9% | 1.47 [0.73, 2.98] |
| Bukstein 1998 | 0.0814 | 0.3335 | 18 | 18 | 12.7% | 1.08 [0.56, 2.09] |
| Chronis 2003 | -1.204 | 1.1995 | 21 | 21 | 1.0% | 0.30 [0.03, 3.15] |
| DuPaul 1996 | -0.1887 | 0.2894 | 24 | 24 | 16.9% | 0.83 [0.47, 1.46] |
| Findling 2007 | 0.4796 | 0.9908 | 16 | 16 | 1.4% | 1.62 [0.23, 11.26] |
| Fine 1993 | 0.2948 | 0.4109 | 12 | 12 | 8.4% | 1.34 [0.60, 3.00] |
| Musten 1997 | -0.0621 | 0.2541 | 31 | 31 | 21.9% | 0.94 [0.57, 1.55] |
| Pearson 2013 | -0.7376 | 1.2605 | 24 | 24 | 0.9% | 0.48 [0.04, 5.66] |
| Pelham 1990a | -0.7419 | 1.264 | 22 | 22 | 0.9% | 0.48 [0.04, 5.67] |
| Pelham 1999 | -1.1386 | 1.6573 | 25 | 25 | 0.5% | 0.32 [0.01, 8.25] |
| Pelham 2005 | 0 | 1.4343 | 36 | 36 | 0.7% | 1.00 [0.06, 16.63] |
| Smith 1998 | 0.5199 | 0.5154 | 45 | 45 | 5.3% | 1.68 [0.61, 4.62] |
| Stein 1996 | -0.5055 | 0.719 | 25 | 25 | 2.7% | 0.60 [0.15, 2.47] |
| Stein 2003 | 0.5573 | 0.5353 | 47 | 47 | 4.9% | 1.75 [0.61, 4.99] |
| Zeni 2009 | 0.5609 | 0.3614 | 16 | 16 | 10.8% | 1.75 [0.86, 3.56] |
| **Subtotal (95% CI)** | | | **444** | **444** | **100.0%** | **1.12 [0.88, 1.41]** |

Heterogeneity: Tau² = 0.00; Chi² = 8.76, df = 14 (P = 0.85); I² = 0%
Test for overall effect: Z = 0.92 (P = 0.36)

### 8.3.18 Repetitive language

| | | | | | | |
|---|---|---|---|---|---|---|
| Pearson 2013 | 0 | 0.5774 | 24 | 24 | 100.0% | 1.00 [0.32, 3.10] |
| **Subtotal (95% CI)** | | | **24** | **24** | **100.0%** | **1.00 [0.32, 3.10]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

Test for overall effect: Z = 0.00 (P = 1.00)

**8.3.19 Sad, tearful or depressed**

| | | | | | | |
|---|---|---|---|---|---|---|
| Barkley 1989 | -0.05 | 0.3164 | 82 | 82 | 11.0% | 0.95 [0.51, 1.77] |
| Buitelaar 1995 | 0.3448 | 0.7926 | 26 | 11 | 1.8% | 1.41 [0.30, 6.67] |
| Chronis 2003 | -0.7444 | 1.266 | 21 | 21 | 0.7% | 0.48 [0.04, 5.68] |
| DuPaul 1996 | -0.145 | 1.0039 | 24 | 24 | 1.1% | 0.87 [0.12, 6.19] |
| Findling 2007 | -0.7621 | 1.2799 | 16 | 16 | 0.7% | 0.47 [0.04, 5.73] |
| Fine 1993 | 0.4139 | 0.4134 | 12 | 12 | 6.4% | 1.51 [0.67, 3.40] |
| Fitzpatrick 1992a | 0.7503 | 1.2706 | 19 | 19 | 0.7% | 2.12 [0.18, 25.55] |
| Gadow 2007 | 0.0987 | 0.2542 | 31 | 31 | 17.0% | 1.10 [0.67, 1.82] |
| Klorman 1990 | 0 | 1.0215 | 48 | 48 | 1.1% | 1.00 [0.14, 7.40] |
| Manos 1999 | -0.2261 | 0.3895 | 177 | 177 | 7.3% | 0.80 [0.37, 1.71] |
| McBride 1988a | 2.3838 | 1.0761 | 48 | 48 | 1.0% | 10.85 [1.32, 89.38] |
| Musten 1997 | 1.543 | 0.6075 | 41 | 41 | 3.0% | 4.68 [1.42, 15.39] |
| Pearson 2013 | 0.3365 | 0.8252 | 24 | 24 | 1.6% | 1.40 [0.28, 7.06] |
| Pelham 1990a | -1.1441 | 1.6606 | 22 | 22 | 0.4% | 0.32 [0.01, 8.25] |
| Pelham 1999 | 0.7841 | 0.9171 | 25 | 25 | 1.3% | 2.19 [0.36, 13.22] |
| Pelham 2005 | 2.5452 | 1.497 | 36 | 36 | 0.5% | 12.75 [0.68, 239.67] |
| Ramtvedt 2013 | 0.0489 | 0.2426 | 34 | 34 | 18.7% | 1.05 [0.65, 1.69] |
| Rapport 2008 | -1.6404 | 1.5592 | 65 | 65 | 0.5% | 0.19 [0.01, 4.12] |
| Sharp 1999 | -0.2019 | 0.45 | 48 | 48 | 5.4% | 0.82 [0.34, 1.97] |
| Smith 1998 | -0.3118 | 0.7947 | 45 | 45 | 1.7% | 0.73 [0.15, 3.48] |
| Stein 1996 | -0.4953 | 0.5778 | 25 | 25 | 3.3% | 0.61 [0.20, 1.89] |
| Stein 2003 | 0.4344 | 0.4185 | 47 | 47 | 6.3% | 1.54 [0.68, 3.51] |
| Zeni 2009 | 0.3662 | 0.3569 | 16 | 16 | 8.6% | 1.44 [0.72, 2.90] |
| **Subtotal (95% CI)** | | | **932** | **917** | **100.0%** | **1.15 [0.94, 1.41]** |

Heterogeneity: Tau² = 0.00; Chi² = 20.95, df = 22 (P = 0.52); I² = 0%
Test for overall effect: Z = 1.35 (P = 0.18)

**8.3.20 Socially withdrawn - decreased interaction with others**

| | | | | | | |
|---|---|---|---|---|---|---|
| Barkley 1989 | -0.2669 | 0.4233 | 82 | 82 | 13.4% | 0.77 [0.33, 1.76] |
| Buitelaar 1995 | 0.8531 | 1.5899 | 26 | 11 | 1.7% | 2.35 [0.10, 52.94] |
| Chronis 2003 | -0.7444 | 1.266 | 21 | 21 | 2.5% | 0.48 [0.04, 5.68] |
| DuPaul 1996 | 0.5805 | 0.6628 | 24 | 24 | 7.5% | 1.79 [0.49, 6.55] |
| Fine 1993 | 0.0483 | 0.4083 | 12 | 12 | 13.9% | 1.05 [0.47, 2.34] |
| Pelham 1999 | -0.4499 | 0.9603 | 25 | 25 | 4.1% | 0.64 [0.10, 4.19] |
| Pelham 2005 | 2.0317 | 1.5307 | 36 | 36 | 1.8% | 7.63 [0.38, 153.21] |
| Ramtvedt 2013 | 0.1482 | 0.2429 | 34 | 34 | 21.0% | 1.16 [0.72, 1.87] |
| Smith 1998 | -0.7161 | 1.2434 | 45 | 45 | 2.6% | 0.49 [0.04, 5.59] |
| Stein 1996 | -1.4979 | 0.8613 | 25 | 25 | 5.0% | 0.22 [0.04, 1.21] |
| Stein 2003 | 0.5242 | 0.462 | 47 | 47 | 12.1% | 1.69 [0.68, 4.18] |
| Zeni 2009 | 1.2716 | 0.3922 | 16 | 16 | 14.5% | 3.57 [1.65, 7.69] |
| **Subtotal (95% CI)** | | | **393** | **378** | **100.0%** | **1.24 [0.82, 1.87]** |

Heterogeneity: Tau² = 0.15; Chi² = 16.66, df = 11 (P = 0.12); I² = 34%
Test for overall effect: Z = 1.01 (P = 0.31)

**8.3.21 Sleep efficiency (SEF)**

| | | | | | | |
|---|---|---|---|---|---|---|
| Schwartz 2004 | -0.8163 | 2.053 | 44 | 44 | 71.5% | 0.44 [0.01, 24.72] |
| Tirosh 1993b | -0.5623 | 3.254 | 10 | 10 | 28.5% | 0.57 [0.00, 335.43] |
| **Subtotal (95% CI)** | | | **54** | **54** | **100.0%** | **0.48 [0.02, 14.28]** |

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.67)

**8.3.22 Stares a lot**

| | | | | | | |
|---|---|---|---|---|---|---|
| Barkley 1989 | -0.0516 | 0.3211 | 82 | 82 | 18.5% | 0.95 [0.51, 1.78] |
| DuPaul 1996 | 0.031 | 1.0056 | 24 | 24 | 2.4% | 1.03 [0.14, 7.40] |
| Findling 2007 | 0.0013 | 1.069 | 16 | 16 | 2.2% | 1.00 [0.12, 8.14] |
| Manos 1999 | -1.1079 | 0.4874 | 177 | 177 | 9.3% | 0.33 [0.13, 0.86] |
| Musten 1997 | 0.1802 | 0.2213 | 41 | 41 | 30.6% | 1.20 [0.78, 1.85] |
| Pearson 2013 | -0.7885 | 0.9195 | 24 | 24 | 2.9% | 0.45 [0.07, 2.76] |
| Stein 1996 | 0.1784 | 0.5979 | 25 | 25 | 6.5% | 1.20 [0.37, 3.86] |
| Stein 2003 | 0 | 0.4127 | 47 | 47 | 12.4% | 1.00 [0.45, 2.25] |
| Zeni 2009 | 0.6164 | 0.363 | 16 | 16 | 15.3% | 1.85 [0.91, 3.77] |
| **Subtotal (95% CI)** | | | **452** | **452** | **100.0%** | **1.03 [0.75, 1.40]** |

Heterogeneity: Tau² = 0.03; Chi² = 9.42, df = 8 (P = 0.31); I² = 15%
Test for overall effect: Z = 0.16 (P = 0.87)

**8.3.23 Tics or nervous movements**

| | | | | | | |
|---|---|---|---|---|---|---|
| Barkley 1989 | 0.5546 | 0.3769 | 82 | 82 | 9.9% | 1.74 [0.83, 3.64] |
| Borcherding 1990 | 0.9433 | 0.363 | 45 | 45 | 10.5% | 2.57 [1.26, 5.23] |
| Buitelaar 1995 | 1.2313 | 1.5541 | 26 | 11 | 0.7% | 3.43 [0.16, 72.04] |
| Chronis 2003 | -0.7444 | 1.266 | 21 | 21 | 1.0% | 0.48 [0.04, 5.68] |
| Findling 2007 | 1.7386 | 1.5905 | 16 | 16 | 0.7% | 5.69 [0.25, 128.50] |
| Gadow 2007 | 0.05492 | 0.9894 | 71 | 71 | 1.7% | 1.06 [0.15, 7.35] |
| Musten 1997 | 0.2598 | 0.2218 | 41 | 41 | 21.6% | 1.30 [0.84, 2.00] |
| Pearson 2013 | 1.1403 | 1.6583 | 24 | 24 | 0.6% | 3.13 [0.12, 80.68] |
| Pelham 1990a | 0.7419 | 1.264 | 22 | 22 | 1.0% | 2.10 [0.18, 25.01] |
| Pelham 1999 | -1.6911 | 1.5754 | 25 | 25 | 0.7% | 0.18 [0.01, 4.04] |
| Pelham 2001a | 2.2574 | 1.5008 | 68 | 68 | 0.7% | 9.56 [0.50, 181.08] |

| | | | | | | |
|---|---|---|---|---|---|---|
| Quinn 2004 | -1.1676 | 1.1842 | 31 | 31 | 1.2% | 0.31 [0.03, 3.17] |
| Ramtvedt 2013 | 0 | 0.2425 | 34 | 34 | 19.3% | 1.00 [0.62, 1.61] |
| Sharp 1999 | 0.7773 | 0.5222 | 48 | 48 | 5.6% | 2.18 [0.78, 6.05] |
| Smith 1998 | -0.7958 | 0.653 | 45 | 45 | 3.7% | 0.45 [0.13, 1.62] |
| Stein 1996 | -0.6061 | 0.793 | 25 | 25 | 2.6% | 0.55 [0.12, 2.58] |
| Stein 2003 | -0.1438 | 0.5367 | 47 | 47 | 5.3% | 0.87 [0.30, 2.48] |
| Tannock 1993 | 1.5404 | 0.8715 | 22 | 22 | 2.2% | 4.67 [0.85, 25.75] |
| Zeni 2009 | 0.2995 | 0.3558 | 16 | 16 | 10.9% | 1.35 [0.67, 2.71] |
| **Subtotal (95% CI)** | | | **709** | **694** | **100.0%** | **1.33 [1.03, 1.72]** |

Heterogeneity: Tau² = 0.03; Chi² = 19.92, df = 18 (P = 0.34); I² = 10%
Test for overall effect: Z = 2.20 (P = 0.03)

**8.3.24 Unusual blinking**

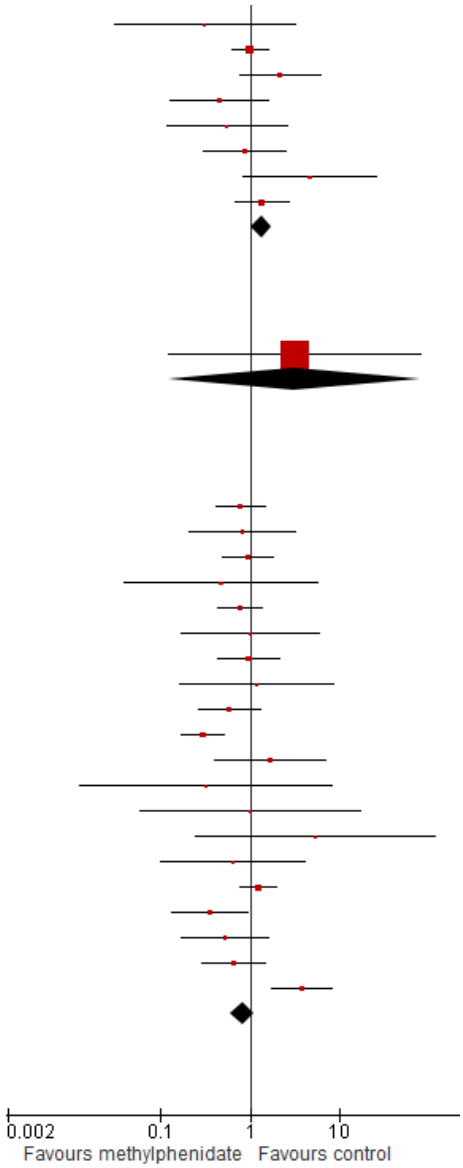
| | | | | | | |
|---|---|---|---|---|---|---|
| Pearson 2013 | 1.1403 | 1.6583 | 24 | 24 | 100.0% | 3.13 [0.12, 80.68] |
| **Subtotal (95% CI)** | | | **24** | **24** | **100.0%** | **3.13 [0.12, 80.68]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)

**8.3.25 Worried or anxious**

| | | | | | | |
|---|---|---|---|---|---|---|
| Barkley 1989 | -0.2472 | 0.3149 | 82 | 82 | 8.3% | 0.78 [0.42, 1.45] |
| Buitelaar 1995 | -0.2007 | 0.6885 | 26 | 11 | 3.8% | 0.82 [0.21, 3.15] |
| Bukstein 1998 | -0.0629 | 0.3334 | 18 | 18 | 8.0% | 0.94 [0.49, 1.80] |
| Chronis 2003 | -0.7444 | 1.266 | 21 | 21 | 1.4% | 0.48 [0.04, 5.68] |
| DuPaul 1996 | -0.2589 | 0.29 | 24 | 24 | 8.7% | 0.77 [0.44, 1.36] |
| Findling 2007 | 0 | 0.9058 | 0 | 0 | 2.5% | 1.00 [0.17, 5.90] |
| Fine 1993 | -0.0299 | 0.4083 | 12 | 12 | 6.8% | 0.97 [0.44, 2.16] |
| Kollins 2006 (PATS) | 0.1648 | 1.0069 | 136 | 160 | 2.1% | 1.18 [0.16, 8.48] |
| Manos 1999 | -0.5356 | 0.3985 | 177 | 177 | 7.0% | 0.59 [0.27, 1.28] |
| Musten 1997 | -1.2106 | 0.2777 | 31 | 31 | 8.9% | 0.30 [0.17, 0.51] |
| Pearson 2013 | 0.5108 | 0.7226 | 24 | 24 | 3.5% | 1.67 [0.40, 6.87] |
| Pelham 1990a | -1.1441 | 1.6606 | 22 | 22 | 0.9% | 0.32 [0.01, 8.25] |
| Pelham 1999 | 0 | 1.4434 | 25 | 25 | 1.1% | 1.00 [0.06, 16.93] |
| Pelham 2005 | 1.6658 | 1.5673 | 36 | 36 | 1.0% | 5.29 [0.25, 114.17] |
| Quinn 2004 | -0.4406 | 0.9505 | 31 | 31 | 2.3% | 0.64 [0.10, 4.15] |
| Ramtvedt 2013 | 0.2118 | 0.2433 | 34 | 34 | 9.5% | 1.24 [0.77, 1.99] |
| Smith 1998 | -1.0325 | 0.4966 | 45 | 45 | 5.6% | 0.36 [0.13, 0.94] |
| Stein 1996 | -0.6466 | 0.5736 | 25 | 25 | 4.8% | 0.52 [0.17, 1.61] |
| Stein 2003 | -0.4279 | 0.4153 | 47 | 47 | 6.7% | 0.65 [0.29, 1.47] |
| Zeni 2009 | 1.3363 | 0.396 | 16 | 16 | 7.0% | 3.80 [1.75, 8.27] |
| **Subtotal (95% CI)** | | | **832** | **841** | **100.0%** | **0.82 [0.60, 1.12]** |

Heterogeneity: Tau² = 0.22; Chi² = 39.12, df = 19 (P = 0.004); I² = 51%
Test for overall effect: Z = 1.23 (P = 0.22)




Test for subgroup differences: Chi² = 71.63, df = 24 (P < 0.00001), I² = 66.5%

**8.4 Digestive system**

| Study or Subgroup | log[Risk Ratio] | SE | Methylphenidate Total | Control Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **8.4.1 Decreased appetite or loss of appetite** | | | | | | |
| Barkley 1989 | 2.0087 | 0.3836 | 82 | 82 | 5.5% | 7.45 [3.51, 15.81] |
| Brams 2012 | 3.0829 | 1.4519 | 163 | 159 | 0.8% | 21.82 [1.27, 375.62] |
| Buitelaar 1995 | -0.2007 | 0.9521 | 26 | 11 | 1.6% | 0.82 [0.13, 5.29] |
| Bukstein 1998 | 1.034 | 0.1374 | 18 | 18 | 9.2% | 2.81 [2.15, 3.68] |
| Castellanos 1997 | 1.1987 | 1.1973 | 22 | 22 | 1.1% | 3.32 [0.32, 34.65] |
| Chacko 2005 | 1.8777 | 0.8172 | 36 | 36 | 2.1% | 6.54 [1.32, 32.44] |
| Chronis 2003 | 0.47 | 0.6905 | 21 | 21 | 2.7% | 1.60 [0.41, 6.19] |
| DuPaul 1996 | 0.744 | 1.101 | 24 | 24 | 1.3% | 2.10 [0.24, 18.21] |
| Findling 2007 | 1.9196 | 1.1652 | 16 | 16 | 1.1% | 6.82 [0.69, 66.91] |
| Fine 1993 | 0.7101 | 0.4234 | 12 | 12 | 5.0% | 2.03 [0.89, 4.66] |
| Fitzpatrick 1992a | 1.2164 | 1.2047 | 19 | 19 | 1.1% | 3.38 [0.32, 35.79] |
| Klorman 1990 | 1.1614 | 0.5734 | 48 | 48 | 3.5% | 3.19 [1.04, 9.83] |
| Kollins 2006 (PATS) | 0.0092 | 0.4119 | 136 | 160 | 5.1% | 1.01 [0.45, 2.26] |
| Manos 1999 | 0.9993 | 0.375 | 177 | 177 | 5.6% | 2.72 [1.30, 5.66] |
| McBride 1988a | 2.0825 | 1.0902 | 48 | 48 | 1.3% | 8.02 [0.95, 67.98] |
| McGough 2006 | 1.6346 | 1.5573 | 80 | 80 | 0.7% | 5.13 [0.24, 108.51] |
| Muniz 2008 | 1.0986 | 1.6403 | 84 | 83 | 0.6% | 3.00 [0.12, 74.70] |
| Musten 1997 | 1.1853 | 0.2404 | 41 | 41 | 7.6% | 3.27 [2.04, 5.24] |
| Pearson 2013 | 2.6247 | 1.1051 | 24 | 24 | 1.2% | 13.80 [1.58, 120.38] |
| Pelham 1990a | 1.4061 | 0.6649 | 22 | 22 | 2.8% | 4.08 [1.11, 15.02] |
| Pelham 1999 | 1.0561 | 0.8908 | 25 | 25 | 1.8% | 2.88 [0.50, 16.48] |
| Pelham 2001a | 1.5353 | 0.6708 | 68 | 68 | 2.8% | 4.64 [1.25, 17.29] |
| Pelham 2005 | 2.3812 | 0.8039 | 36 | 36 | 2.1% | 10.82 [2.24, 52.29] |
| Pelham 2011 | 0.539 | 1.0494 | 10 | 10 | 1.4% | 1.71 [0.22, 13.41] |
| Ramtvedt 2013 | 0.5487 | 0.2473 | 34 | 34 | 7.5% | 1.73 [1.07, 2.81] |
| Rapport 2008 | 0.745 | 0.4416 | 65 | 65 | 4.8% | 2.11 [0.89, 5.01] |
| Schulz 2010 | 0.4055 | 0.9204 | 147 | 146 | 1.7% | 1.50 [0.25, 9.11] |

| | | | | | | |
|---|---|---|---|---|---|---|
| Sharp 1999 | 4.1607 | 1.4511 | 48 | 48 | 0.8% | 64.12 [3.73, 1101.91] |
| Silva 2006 | 2.4941 | 1.4901 | 54 | 54 | 0.7% | 12.11 [0.65, 224.67] |
| Stein 1996 | 1.6982 | 0.6183 | 25 | 25 | 3.1% | 5.46 [1.63, 18.36] |
| Stein 2003 | 1.7318 | 0.4546 | 47 | 47 | 4.6% | 5.65 [2.32, 13.77] |
| Stein 2011 | 1.2192 | 1.1755 | 42 | 45 | 1.1% | 3.38 [0.34, 33.89] |
| Swanson 2004b | 1.831 | 1.0853 | 181 | 183 | 1.3% | 6.24 [0.74, 52.36] |
| Wilens 2010 | 3.8514 | 1.4711 | 30 | 30 | 0.7% | 47.06 [2.63, 841.09] |
| Zeni 2009 | -0.1902 | 0.3545 | 16 | 16 | 5.9% | 0.83 [0.41, 1.66] |
| **Subtotal (95% CI)** | | | **1927** | **1935** | **100.0%** | **3.04 [2.35, 3.94]** |

Heterogeneity: Tau² = 0.17; Chi² = 56.81, df = 34 (P = 0.008); I² = 40%
Test for overall effect: Z = 8.47 (P < 0.00001)

### 8.4.2 Diarrhoea

| | | | | | | |
|---|---|---|---|---|---|---|
| Pelham 2001a | -1.1133 | 1.642 | 68 | 68 | 11.7% | 0.33 [0.01, 8.21] |
| Rapport 2008 | -0.2397 | 0.695 | 65 | 65 | 65.2% | 0.79 [0.20, 3.07] |
| Silva 2008 | -1.1289 | 1.1678 | 68 | 68 | 23.1% | 0.32 [0.03, 3.19] |
| **Subtotal (95% CI)** | | | **201** | **201** | **100.0%** | **0.58 [0.19, 1.74]** |

Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 2 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.97 (P = 0.33)

### 8.4.3 Dry mouth

| | | | | | | |
|---|---|---|---|---|---|---|
| Carlson 1995 | 1.182 | 1.6833 | 12 | 12 | 6.5% | 3.26 [0.12, 88.34] |
| Klorman 1990 | 1.4523 | 1.1375 | 48 | 48 | 14.1% | 4.27 [0.46, 39.72] |
| Pearson 2013 | 1.6946 | 1.5765 | 24 | 24 | 7.4% | 5.44 [0.25, 119.64] |
| Pelham 1990a | 0 | 1.4475 | 22 | 22 | 8.7% | 1.00 [0.06, 17.07] |
| Rapport 2008 | -0.2864 | 0.5376 | 65 | 65 | 63.3% | 0.75 [0.26, 2.15] |
| **Subtotal (95% CI)** | | | **171** | **171** | **100.0%** | **1.25 [0.54, 2.90]** |

Heterogeneity: Tau² = 0.00; Chi² = 3.29, df = 4 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.53 (P = 0.60)

### 8.4.4 Dyspepsia

| | | | | | | |
|---|---|---|---|---|---|---|
| Quinn 2004 | -1.4917 | 1.1491 | 31 | 31 | 100.0% | 0.22 [0.02, 2.14] |
| **Subtotal (95% CI)** | | | **31** | **31** | **100.0%** | **0.22 [0.02, 2.14]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.30 (P = 0.19)

### 8.4.5 Nausea

| | | | | | | |
|---|---|---|---|---|---|---|
| Buitelaar 1995 | -0.2007 | 0.9521 | 26 | 11 | 4.9% | 0.82 [0.13, 5.29] |
| Carlson 1995 | 1.182 | 1.6833 | 12 | 12 | 1.6% | 3.26 [0.12, 88.34] |
| Fitzpatrick 1992a | 1.1513 | 1.6649 | 19 | 19 | 1.6% | 3.16 [0.12, 82.64] |
| Klorman 1990 | -1.1194 | 1.6457 | 48 | 48 | 1.6% | 0.33 [0.01, 8.22] |
| McGough 2006 | 1.9839 | 1.5202 | 80 | 80 | 1.9% | 7.27 [0.37, 143.08] |
| Muniz 2008 | 1.0986 | 1.6403 | 84 | 83 | 1.7% | 3.00 [0.12, 74.70] |
| Pearson 2013 | 0 | 1.4446 | 24 | 24 | 2.1% | 1.00 [0.06, 16.97] |
| Ramtvedt 2013 | 0.3894 | 0.245 | 34 | 34 | 74.1% | 1.48 [0.91, 2.39] |
| Rapport 2008 | 0.61 | 0.6531 | 65 | 65 | 10.4% | 1.84 [0.51, 6.62] |
| **Subtotal (95% CI)** | | | **392** | **376** | **100.0%** | **1.52 [1.00, 2.30]** |

Heterogeneity: Tau² = 0.00; Chi² = 3.11, df = 8 (P = 0.93); I² = 0%
Test for overall effect: Z = 1.98 (P = 0.05)

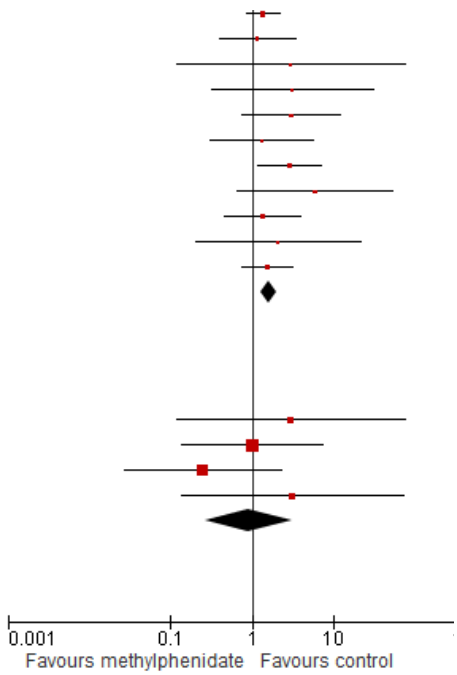
### 8.4.6 Increased appetite

| | | | | | | |
|---|---|---|---|---|---|---|
| Pelham 2001a | -1.6226 | 0.4717 | 68 | 68 | 100.0% | 0.20 [0.08, 0.50] |
| **Subtotal (95% CI)** | | | **68** | **68** | **100.0%** | **0.20 [0.08, 0.50]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 3.44 (P = 0.0006)

### 8.4.7 Stomachache

| | | | | | | |
|---|---|---|---|---|---|---|
| Barkley 1989 | 0.8936 | 0.3673 | 82 | 82 | 6.6% | 2.44 [1.19, 5.02] |
| Brams 2008 | -0.2998 | 0.7795 | 86 | 86 | 2.1% | 0.74 [0.16, 3.41] |
| Brams 2012 | 0.163 | 0.6161 | 163 | 159 | 3.1% | 1.18 [0.35, 3.94] |
| Buitelaar 1995 | -1.0561 | 0.9139 | 26 | 11 | 1.6% | 0.35 [0.06, 2.09] |
| Bukstein 1998 | 1.2335 | 0.2601 | 18 | 18 | 9.4% | 3.43 [2.06, 5.72] |
| Carlson 1995 | 0.5108 | 1.022 | 12 | 12 | 1.3% | 1.67 [0.22, 12.35] |
| Chronis 2003 | -0.3448 | 0.8353 | 21 | 21 | 1.8% | 0.71 [0.14, 3.64] |
| DuPaul 1996 | 0.39908 | 0.7796 | 24 | 24 | 2.1% | 1.49 [0.32, 6.87] |
| Findling 2007 | 1.2417 | 1.2153 | 16 | 16 | 0.9% | 3.46 [0.32, 37.47] |
| Fine 1993 | 0.4263 | 0.4138 | 12 | 12 | 5.6% | 1.53 [0.68, 3.45] |
| Fitzpatrick 1992a | 1.1513 | 1.6649 | 19 | 19 | 0.5% | 3.16 [0.12, 82.64] |
| Klorman 1990 | 0 | 0.8433 | 48 | 48 | 1.8% | 1.00 [0.19, 5.22] |
| Kollins 2006 (PATS) | -0.5411 | 0.874 | 136 | 160 | 1.7% | 0.58 [0.10, 3.23] |
| Manos 1999 | 1.525 | 0.5664 | 177 | 177 | 3.6% | 4.60 [1.51, 13.95] |
| Muniz 2008 | 1.0986 | 1.6403 | 84 | 83 | 0.5% | 3.00 [0.12, 74.70] |
| Murray 2011 | 0.7244 | 0.8839 | 67 | 67 | 1.7% | 2.06 [0.36, 11.67] |
| Musten 1997 | -0.2844 | 0.222 | 41 | 41 | 10.7% | 0.75 [0.49, 1.16] |
| Pearson 2013 | 1.1896 | 1.1935 | 24 | 24 | 1.0% | 3.29 [0.32, 34.08] |
| Pelham 1990a | -0.4568 | 0.9675 | 22 | 22 | 1.4% | 0.63 [0.10, 4.22] |
| Pelham 1999 | 1.6911 | 1.5754 | 25 | 25 | 0.6% | 5.43 [0.25, 118.96] |
| Pelham 2001a | 0.1346 | 0.5194 | 68 | 68 | 4.1% | 1.14 [0.41, 3.17] |
| Pelham 2005 | 2.0317 | 1.5307 | 36 | 36 | 0.6% | 7.63 [0.38, 153.21] |



| | | | | | | |
|---|---|---|---|---|---|---|
| Ramtvedt 2013 | 0.3042 | 0.244 | 34 | 34 | 10.0% | 1.36 [0.84, 2.19] |
| Rapport 2008 | 0.1509 | 0.5501 | 65 | 65 | 3.7% | 1.16 [0.40, 3.42] |
| Schulz 2010 | 1.0986 | 1.6372 | 147 | 146 | 0.5% | 3.00 [0.12, 74.25] |
| Silva 2006 | 1.1371 | 1.1712 | 54 | 54 | 1.0% | 3.12 [0.31, 30.96] |
| Smith 1998 | 1.1076 | 0.7136 | 45 | 45 | 2.4% | 3.03 [0.75, 12.26] |
| Stein 1996 | 0.2719 | 0.74 | 25 | 25 | 2.3% | 1.31 [0.31, 5.60] |
| Stein 2003 | 1.0578 | 0.4518 | 47 | 47 | 5.0% | 2.88 [1.19, 6.98] |
| Stein 2011 | 1.7827 | 1.1179 | 42 | 45 | 1.1% | 5.95 [0.66, 53.18] |
| Swanson 2004b | 0.3105 | 0.5505 | 181 | 183 | 3.7% | 1.36 [0.46, 4.01] |
| Wigal 2014 | 0.7397 | 1.1861 | 21 | 22 | 1.0% | 2.10 [0.20, 21.42] |
| Zeni 2009 | 0.429 | 0.3582 | 16 | 16 | 6.8% | 1.54 [0.76, 3.10] |
| **Subtotal (95% CI)** | | | **1884** | **1893** | **100.0%** | **1.61 [1.27, 2.04]** |

Heterogeneity: Tau² = 0.09; Chi² = 41.01, df = 32 (P = 0.13); I² = 22%
Test for overall effect: Z = 3.97 (P < 0.0001)

**8.4.8 Vomiting**

| | | | | | | |
|---|---|---|---|---|---|---|
| Muniz 2008 | 1.0986 | 1.6403 | 84 | 83 | 14.7% | 3.00 [0.12, 74.70] |
| Pelham 2001a | 0 | 1.015 | 68 | 68 | 38.5% | 1.00 [0.14, 7.31] |
| Swanson 2004b | -1.3919 | 1.123 | 181 | 183 | 31.4% | 0.25 [0.03, 2.25] |
| Wigal 2014 | 1.1431 | 1.6055 | 21 | 22 | 15.4% | 3.14 [0.13, 72.95] |
| **Subtotal (95% CI)** | | | **354** | **356** | **100.0%** | **0.90 [0.26, 3.11]** |

Heterogeneity: Tau² = 0.00; Chi² = 2.47, df = 3 (P = 0.48); I² = 0%
Test for overall effect: Z = 0.16 (P = 0.87)



Test for subgroup differences: Chi² = 48.70, df = 7 (P < 0.00001), I² = 85.6%

**8.5 Urinary system: urinary incontinence**

| | Methylphenidate | | Control | | Risk Ratio | Risk Ratio |
|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | IV, Random, 95% CI | IV, Random, 95% CI |
| Pelham 2001a | 1 | 68 | 2 | 68 | 0.50 [0.05, 5.39] | |

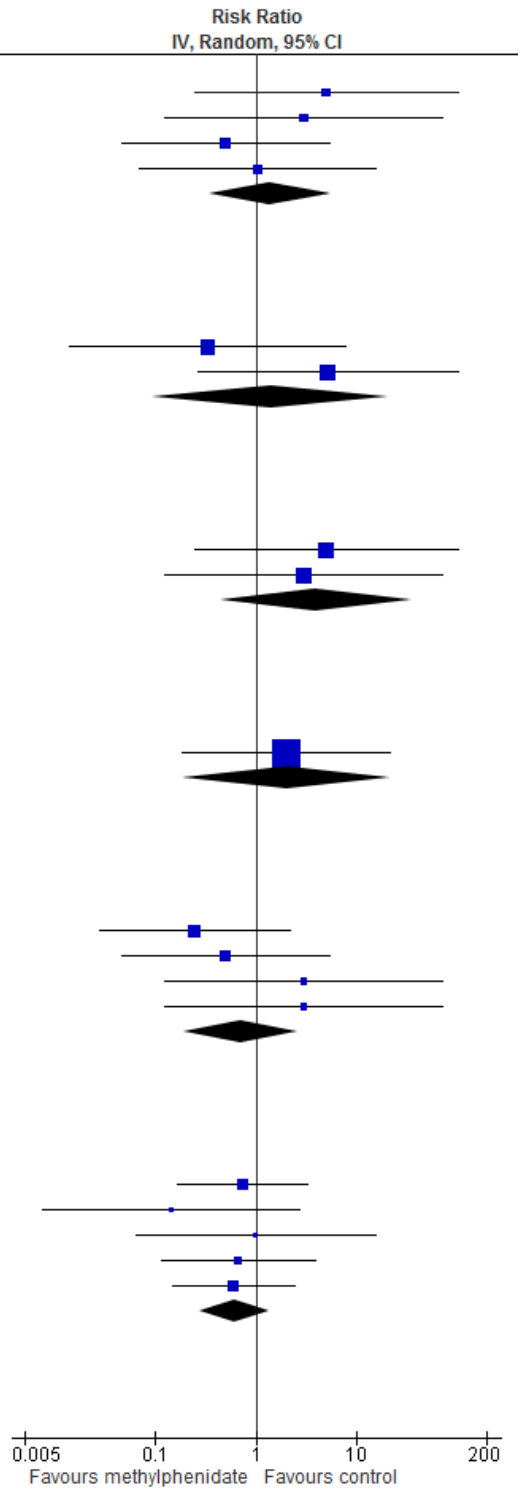


**8.6 Skeletal and muscular system: somatic complaints**

| | Methylphenidate | | | Control | | | Mean Difference | Mean Difference |
|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | IV, Random, 95% CI | IV, Random, 95% CI |
| Gorman 2006 | 1.14 | 0.15 | 41 | 0.29 | 0.1 | 41 | 0.85 [0.79, 0.91] | |

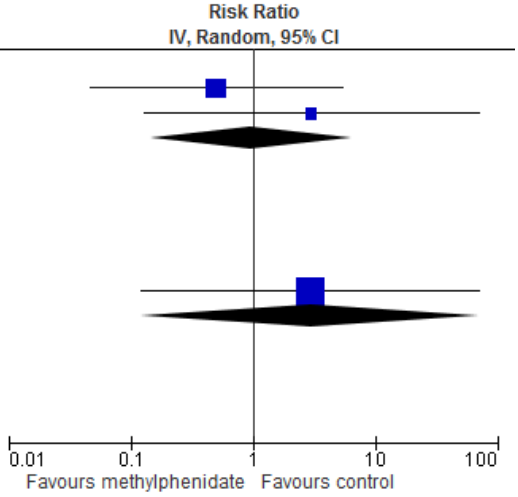
**8.7 Immune system**

| Study or Subgroup | Methylphenidate Events | Total | Control Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **8.7.1 Allergic rhinitis** | | | | | | |
| McGough 2006 | 2 | 80 | 0 | 80 | 21.0% | 5.00 [0.24, 102.53] |
| Pelham 2001a | 1 | 68 | 0 | 68 | 18.9% | 3.00 [0.12, 72.37] |
| Silva 2008 | 1 | 68 | 2 | 68 | 33.9% | 0.50 [0.05, 5.39] |
| Wigal 2014 | 1 | 21 | 1 | 22 | 26.2% | 1.05 [0.07, 15.69] |
| **Subtotal (95% CI)** | | **237** | | **238** | **100.0%** | **1.38 [0.35, 5.51]** |
| Total events | 5 | | 3 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 1.67, df = 3 (P = 0.64); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.46 (P = 0.65) | | | | | | |
| **8.7.2 Fever** | | | | | | |
| Pearson 2013 | 0 | 24 | 1 | 24 | 48.2% | 0.33 [0.01, 7.80] |
| Wigal 2014 | 2 | 21 | 0 | 22 | 51.8% | 5.23 [0.27, 102.87] |
| **Subtotal (95% CI)** | | **45** | | **46** | **100.0%** | **1.39 [0.09, 20.56]** |
| Total events | 2 | | 1 | | | |
| Heterogeneity: Tau² = 1.34; Chi² = 1.55, df = 1 (P = 0.21); I² = 35% | | | | | | |
| Test for overall effect: Z = 0.24 (P = 0.81) | | | | | | |
| **8.7.3 Lymphadenitis** | | | | | | |
| McGough 2006 | 2 | 80 | 0 | 80 | 52.6% | 5.00 [0.24, 102.53] |
| Silva 2008 | 1 | 68 | 0 | 68 | 47.4% | 3.00 [0.12, 72.37] |
| **Subtotal (95% CI)** | | **148** | | **148** | **100.0%** | **3.93 [0.44, 35.11]** |
| Total events | 3 | | 0 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.22 (P = 0.22) | | | | | | |
| **8.7.4 Pharyngolaryngeal pain** | | | | | | |
| McGough 2006 | 2 | 80 | 1 | 80 | 100.0% | 2.00 [0.19, 21.62] |
| **Subtotal (95% CI)** | | **80** | | **80** | **100.0%** | **2.00 [0.19, 21.62]** |
| Total events | 2 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.57 (P = 0.57) | | | | | | |
| **8.7.5 Pharyngitis** | | | | | | |
| Brams 2012 | 1 | 163 | 4 | 159 | 36.0% | 0.24 [0.03, 2.16] |
| McGough 2006 | 1 | 80 | 2 | 80 | 30.2% | 0.50 [0.05, 5.40] |
| Pelham 2001a | 1 | 68 | 0 | 68 | 16.9% | 3.00 [0.12, 72.37] |
| Silva 2008 | 1 | 68 | 0 | 68 | 16.9% | 3.00 [0.12, 72.37] |
| **Subtotal (95% CI)** | | **379** | | **375** | **100.0%** | **0.71 [0.19, 2.62]** |
| Total events | 4 | | 6 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 2.58, df = 3 (P = 0.46); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.52 (P = 0.60) | | | | | | |
| **8.7.6 Upper respiratory tract infection** | | | | | | |
| Brams 2012 | 3 | 163 | 4 | 159 | 29.5% | 0.73 [0.17, 3.22] |
| McGough 2006 | 0 | 80 | 3 | 80 | 7.5% | 0.14 [0.01, 2.72] |
| Murray 2011 | 1 | 67 | 1 | 67 | 8.6% | 1.00 [0.06, 15.66] |
| Pelham 2001a | 2 | 68 | 3 | 68 | 21.0% | 0.67 [0.12, 3.86] |
| Silva 2008 | 3 | 68 | 5 | 68 | 33.5% | 0.60 [0.15, 2.41] |
| **Subtotal (95% CI)** | | **446** | | **442** | **100.0%** | **0.61 [0.27, 1.37]** |
| Total events | 9 | | 16 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 1.12, df = 4 (P = 0.89); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.20 (P = 0.23) | | | | | | |



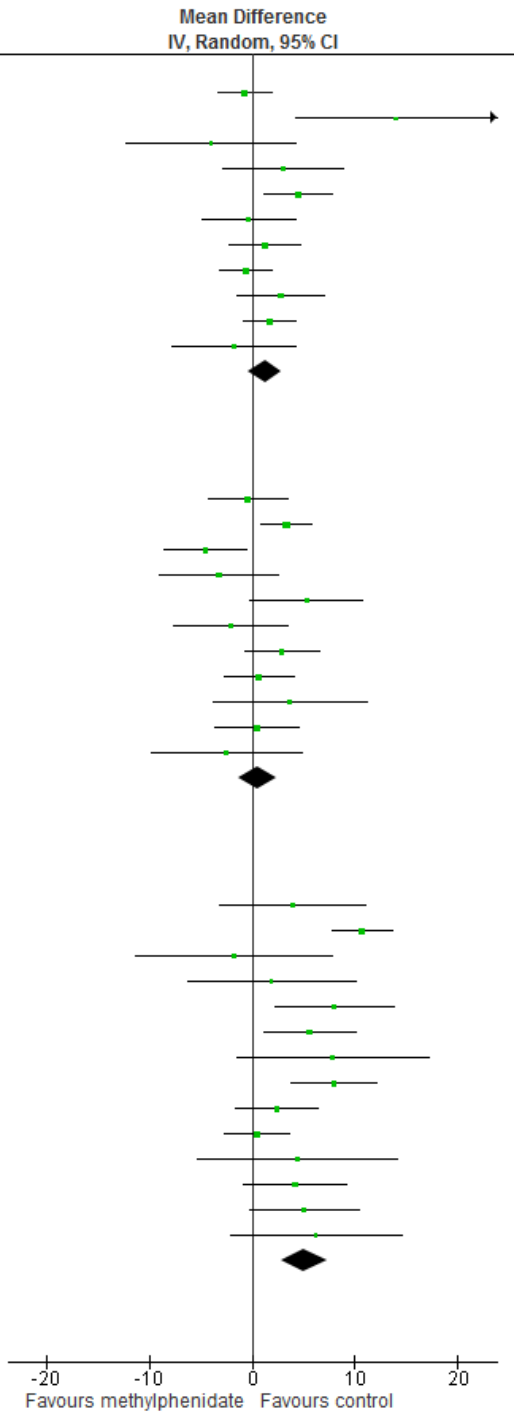
**8.8 Skin**

| Study or Subgroup | Methylphenidate Events | Total | Control Events | Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **8.8.1 Rash** | | | | | | |
| McGough 2006 | 1 | 80 | 2 | 80 | 63.7% | 0.50 [0.05, 5.40] |
| Pearson 2013 | 1 | 24 | 0 | 24 | 36.3% | 3.00 [0.13, 70.16] |
| **Subtotal (95% CI)** | | **104** | | **104** | **100.0%** | **0.96 [0.14, 6.41]** |
| Total events | 2 | | 2 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.79, df = 1 (P = 0.37); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.04 (P = 0.97) | | | | | | |
| **8.8.2 Skin laceration** | | | | | | |
| Muniz 2008 | 1 | 84 | 0 | 83 | 100.0% | 2.96 [0.12, 71.75] |
| **Subtotal (95% CI)** | | **84** | | **83** | **100.0%** | **2.96 [0.12, 71.75]** |
| Total events | 1 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.67 (P = 0.50) | | | | | | |



**8.9 Vital signs**

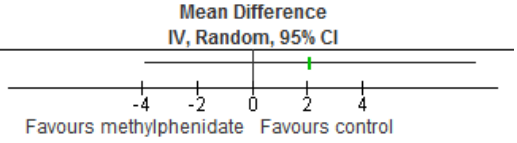
| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **8.9.1 Diastolic blood pressure (mmHg)** | | | | | | | | |
| Brown 1984a | 61.27 | 2.87 | 11 | 62 | 3.35 | 11 | 14.2% | -0.73 [-3.34, 1.88] |
| Brown 1988 | 83 | 4.51 | 11 | 69 | 15.93 | 11 | 2.5% | 14.00 [4.22, 23.78] |
| Brown 1991 | 72 | 12.65 | 22 | 76 | 15.23 | 22 | 3.3% | -4.00 [-12.27, 4.27] |
| Findling 2007 | 64.7 | 8.6 | 20 | 61.7 | 10.4 | 20 | 5.7% | 3.00 [-2.91, 8.91] |
| Gadow 2007 | 64.5 | 11 | 71 | 60 | 9 | 71 | 11.6% | 4.50 [1.19, 7.81] |
| Pearson 2013 | 70.17 | 7.5 | 24 | 70.48 | 8.3 | 24 | 8.3% | -0.31 [-4.79, 4.17] |
| Silva 2005a | 66.8 | 9.6 | 54 | 65.5 | 8.8 | 54 | 11.1% | 1.30 [-2.17, 4.77] |
| Stein 2011 | 63.96 | 9.386 | 90 | 64.53 | 8.57 | 101 | 14.4% | -0.57 [-3.13, 1.99] |
| Tannock 1989 | 66.6 | 5.7 | 12 | 63.8 | 4.8 | 12 | 8.9% | 2.80 [-1.42, 7.02] |
| Urman 1995 | 75.8 | 5.3 | 34 | 74.1 | 5.5 | 34 | 14.4% | 1.70 [-0.87, 4.27] |
| Zeiner 1999 | 66.9 | 12.2 | 23 | 68.7 | 8.1 | 23 | 5.6% | -1.80 [-7.78, 4.18] |
| **Subtotal (95% CI)** | | | **372** | | | **383** | **100.0%** | **1.23 [-0.39, 2.86]** |
| Heterogeneity: Tau² = 3.06; Chi² = 18.25, df = 10 (P = 0.05); I² = 45% | | | | | | | | |
| Test for overall effect: Z = 1.49 (P = 0.14) | | | | | | | | |
| **8.9.2 Systolic blood pressure (mmHg)** | | | | | | | | |
| Brown 1984a | 92.36 | 5.57 | 11 | 92.73 | 3.38 | 11 | 10.7% | -0.37 [-4.22, 3.48] |
| Brown 1988 | 98 | 1.54 | 11 | 94.66 | 3.88 | 11 | 14.9% | 3.34 [0.87, 5.81] |
| Brown 1991 | 119.5 | 8.23 | 22 | 124 | 4.9 | 22 | 10.3% | -4.50 [-8.50, -0.50] |
| Findling 2007 | 114.9 | 11.7 | 20 | 118.1 | 6.2 | 20 | 6.7% | -3.20 [-9.00, 2.60] |
| Gadow 2007 | 104.3 | 15.2 | 71 | 99 | 17.9 | 71 | 7.3% | 5.30 [-0.16, 10.76] |
| Pearson 2013 | 103.6 | 9.4 | 24 | 105.7 | 10.3 | 24 | 7.1% | -2.10 [-7.68, 3.48] |
| Silva 2005a | 104.7 | 9.4 | 54 | 101.8 | 10 | 54 | 11.3% | 2.90 [-0.76, 6.56] |
| Stein 2011 | 103.96 | 12.017 | 90 | 103.25 | 11.725 | 101 | 12.1% | 0.71 [-2.67, 4.09] |
| Tannock 1989 | 104.4 | 9.8 | 12 | 100.7 | 8.9 | 12 | 4.6% | 3.70 [-3.79, 11.19] |
| Urman 1995 | 105 | 9.2 | 34 | 104.5 | 7.8 | 34 | 10.2% | 0.50 [-3.55, 4.55] |
| Zeiner 1999 | 111.8 | 14.3 | 23 | 114.3 | 10.8 | 23 | 4.8% | -2.50 [-9.82, 4.82] |
| **Subtotal (95% CI)** | | | **372** | | | **383** | **100.0%** | **0.53 [-1.30, 2.36]** |
| Heterogeneity: Tau² = 4.28; Chi² = 19.25, df = 10 (P = 0.04); I² = 48% | | | | | | | | |
| Test for overall effect: Z = 0.57 (P = 0.57) | | | | | | | | |
| **8.9.3 Pulse or heart rate (bpm)** | | | | | | | | |
| Brown 1984a | 86.82 | 8.59 | 11 | 82.91 | 8.3 | 11 | 5.7% | 3.91 [-3.15, 10.97] |
| Brown 1988 | 82.5 | 3.2 | 11 | 71.83 | 3.81 | 11 | 11.3% | 10.67 [7.73, 13.61] |
| Brown 1991 | 87.25 | 8.54 | 7 | 89 | 9.63 | 7 | 3.8% | -1.75 [-11.28, 7.78] |
| Findling 2007 | 91.4 | 14.3 | 20 | 89.5 | 12 | 20 | 4.7% | 1.90 [-6.28, 10.08] |
| Gadow 1995 | 93.5 | 13.9 | 34 | 85.5 | 10 | 34 | 7.2% | 8.00 [2.24, 13.76] |
| Gadow 2007 | 91.6 | 14.8 | 71 | 86 | 11.9 | 71 | 9.0% | 5.60 [1.18, 10.02] |
| Pearson 2013 | 97.43 | 15.8 | 24 | 89.57 | 17.3 | 24 | 3.9% | 7.86 [-1.51, 17.23] |
| Rapport 1987 | 94.2 | 11.2 | 47 | 86.2 | 9.3 | 47 | 9.4% | 8.00 [3.84, 12.16] |
| Silva 2005a | 90.6 | 12.4 | 54 | 88.2 | 8.5 | 54 | 9.6% | 2.40 [-1.61, 6.41] |
| Stein 2011 | 73.2 | 9.853 | 89 | 72.72 | 11.801 | 98 | 11.1% | 0.48 [-2.63, 3.59] |
| Tannock 1989 | 96.3 | 12.3 | 12 | 91.9 | 12 | 12 | 3.7% | 4.40 [-5.32, 14.12] |
| Tannock 1995a | 95.9 | 8.9 | 28 | 91.7 | 10.3 | 28 | 8.1% | 4.20 [-0.84, 9.24] |
| Urman 1995 | 91.2 | 12.4 | 34 | 86.1 | 9.8 | 34 | 7.7% | 5.10 [-0.21, 10.41] |
| Zeiner 1999 | 75.8 | 15.5 | 23 | 69.6 | 13.1 | 23 | 4.7% | 6.20 [-2.09, 14.49] |
| **Subtotal (95% CI)** | | | **465** | | | **474** | **100.0%** | **5.06 [2.88, 7.24]** |
| Heterogeneity: Tau² = 8.67; Chi² = 30.01, df = 13 (P = 0.005); I² = 57% | | | | | | | | |
| Test for overall effect: Z = 4.55 (P < 0.00001) | | | | | | | | |




Test for subgroup differences: Chi² = 10.88, df = 2 (P = 0.004), I² = 81.6%

**8.10 Height (cm)**

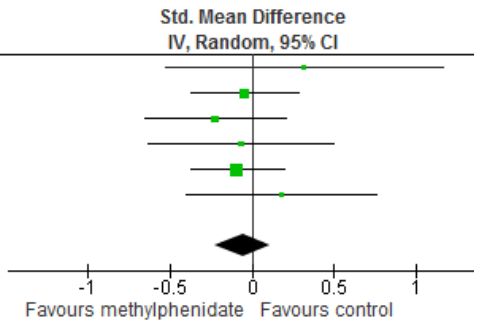
| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| Zeiner 1999 | 150.4 | 11.2 | 23 | 148.3 | 9.4 | 23 | 2.10 [-3.88, 8.08] |



**8.11 Weight**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Brown 1988 | 103.66 | 4.63 | 11 | 102.16 | 4.4 | 11 | 4.1% | 0.32 [-0.52, 1.16] |
| Gadow 2007 | 77.8 | 31.6 | 71 | 79.3 | 32.3 | 71 | 26.9% | -0.05 [-0.38, 0.28] |
| Gorman 2006 | 36.09 | 1.99 | 41 | 36.54 | 2.01 | 41 | 15.4% | -0.22 [-0.66, 0.21] |
| Pearson 2013 | 32.47 | 8.8 | 24 | 33.03 | 8.6 | 24 | 9.1% | -0.06 [-0.63, 0.50] |
| Stein 2011 | 49.716 | 18.9817 | 88 | 51.624 | 22.2636 | 102 | 35.8% | -0.09 [-0.38, 0.19] |
| Zeiner 1999 | 42 | 10.2 | 23 | 40.3 | 8 | 23 | 8.7% | 0.18 [-0.40, 0.76] |
| **Total (95% CI)** | | | **258** | | | **272** | **100.0%** | **-0.06 [-0.23, 0.11]** |

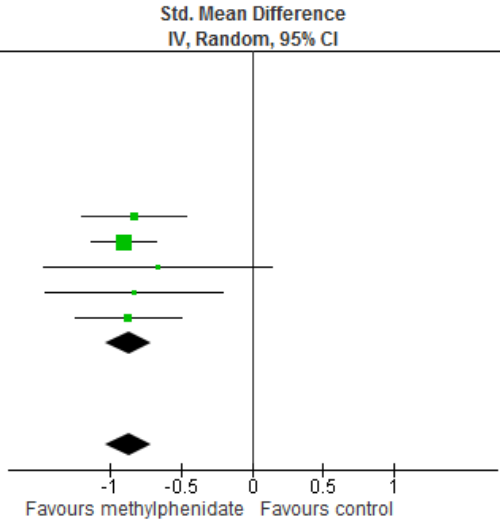
Heterogeneity: Tau² = 0.00; Chi² = 2.04, df = 5 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.65 (P = 0.52)




## 9 - Teacher-rated general behaviour

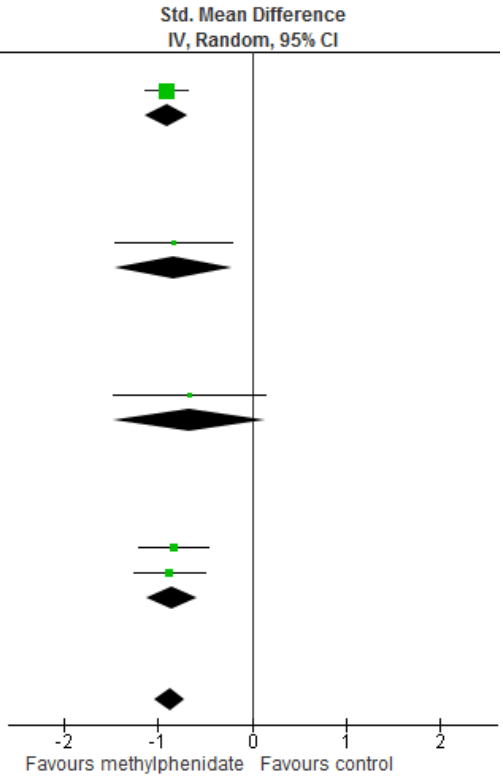
**9.1 All parallel-group trials and first-period cross-over trials: risk of bias**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **9.1.1 Low risk of bias** | | | | | | | | |
| **Subtotal (95% CI)** | | | **0** | | | **0** | | **Not estimable** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | | |
| **9.1.2 High risk of bias** | | | | | | | | |
| Findling 2006 | 2.3 | 2.7386 | 120 | 4.6 | 2.7478 | 39 | 19.6% | -0.84 [-1.21, -0.46] |
| Greenhill 2002 | 4.9 | 4.66 | 155 | 10.3 | 6.92 | 159 | 50.3% | -0.91 [-1.14, -0.68] |
| Ialongo 1994 | 3.07 | 2.78 | 13 | 5.83 | 5 | 12 | 4.1% | -0.67 [-1.48, 0.14] |
| Van der Meere 1999a | 37.8 | 5.8543 | 22 | 42.8 | 5.8543 | 21 | 6.9% | -0.84 [-1.46, -0.21] |
| Wolraich 2001 | 1.78 | 2.99 | 81 | 5.21 | 5.12 | 46 | 19.0% | -0.88 [-1.25, -0.50] |
| **Subtotal (95% CI)** | | | **391** | | | **277** | **100.0%** | **-0.87 [-1.04, -0.71]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 4 (P = 0.98); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 10.39 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **391** | | | **277** | **100.0%** | **-0.87 [-1.04, -0.71]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 4 (P = 0.98); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 10.39 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | |



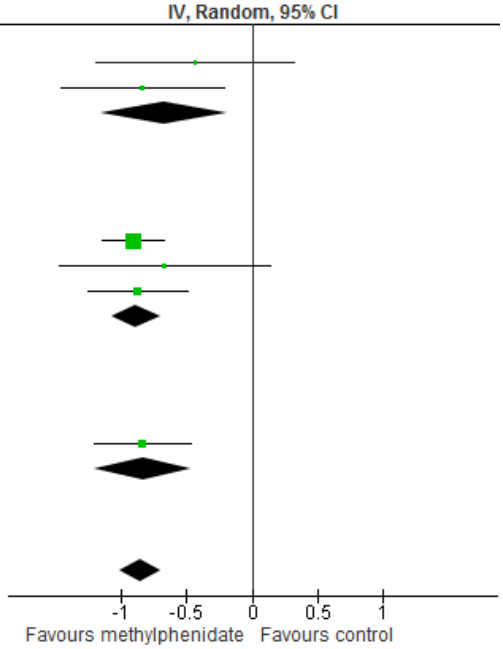

**9.2 Subgroup analysis: types of scales**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **9.2.1 Conners' Global Index - Teacher (CGI-T)** | | | | | | | | |
| Greenhill 2002 | 4.9 | 4.66 | 155 | 10.3 | 6.92 | 159 | 50.3% | -0.91 [-1.14, -0.68] |
| **Subtotal (95% CI)** | | | **155** | | | **159** | **50.3%** | **-0.91 [-1.14, -0.68]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 7.68 (P < 0.00001) | | | | | | | | |
| **9.2.2 Groninger Behaviour Observation Scale (GBOS)** | | | | | | | | |
| Van der Meere 1999a | 37.8 | 5.8543 | 22 | 42.8 | 5.8543 | 21 | 6.9% | -0.84 [-1.46, -0.21] |
| **Subtotal (95% CI)** | | | **22** | | | **21** | **6.9%** | **-0.84 [-1.46, -0.21]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 2.62 (P = 0.009) | | | | | | | | |
| **9.2.3 Conners' Teacher Rating Scale - Conduct problems** | | | | | | | | |
| Ialongo 1994 | 3.07 | 2.78 | 13 | 5.83 | 5 | 12 | 4.1% | -0.67 [-1.48, 0.14] |
| **Subtotal (95% CI)** | | | **13** | | | **12** | **4.1%** | **-0.67 [-1.48, 0.14]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 1.61 (P = 0.11) | | | | | | | | |
| **9.2.4 IOWA Conners' Rating Scale - Oppositional/Defiant (IOWA-O/D)** | | | | | | | | |
| Findling 2006 | 2.3 | 2.7386 | 120 | 4.6 | 2.7478 | 39 | 19.6% | -0.84 [-1.21, -0.46] |
| Wolraich 2001 | 1.78 | 2.99 | 81 | 5.21 | 5.12 | 46 | 19.0% | -0.88 [-1.25, -0.50] |
| **Subtotal (95% CI)** | | | **201** | | | **85** | **38.6%** | **-0.86 [-1.12, -0.59]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 6.31 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **391** | | | **277** | **100.0%** | **-0.87 [-1.04, -0.71]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 4 (P = 0.98); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 10.39 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.38, df = 3 (P = 0.94), I² = 0% | | | | | | | | |



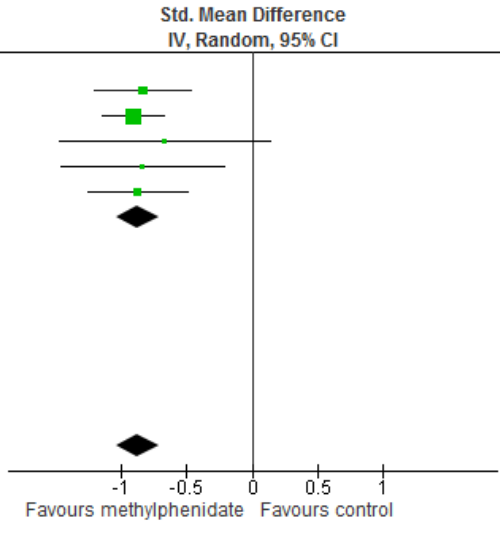
**9.3 Subgroup analysis: dose**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **9.3.1 Low dose** | | | | | | | | |
| Ialongo 1994 | 3.85 | 3.95 | 16 | 5.83 | 5 | 12 | 4.5% | -0.43 [-1.19, 0.32] |
| Van der Meere 1999a | 37.8 | 5.8543 | 22 | 42.8 | 5.8543 | 21 | 6.6% | -0.84 [-1.46, -0.21] |
| **Subtotal (95% CI)** | | | **38** | | | **33** | **11.1%** | **-0.67 [-1.16, -0.19]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.65, df = 1 (P = 0.42); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 2.74 (P = 0.006) | | | | | | | | |
| **9.3.2 High dose** | | | | | | | | |
| Greenhill 2002 | 4.9 | 4.66 | 155 | 10.3 | 6.92 | 159 | 48.0% | -0.91 [-1.14, -0.68] |
| Ialongo 1994 | 3.07 | 2.78 | 13 | 5.83 | 5 | 12 | 4.0% | -0.67 [-1.48, 0.14] |
| Wolraich 2001 | 1.78 | 2.99 | 81 | 5.21 | 5.12 | 46 | 18.2% | -0.88 [-1.25, -0.50] |
| **Subtotal (95% CI)** | | | **249** | | | **217** | **70.2%** | **-0.89 [-1.08, -0.70]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 2 (P = 0.85); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 9.05 (P < 0.00001) | | | | | | | | |
| **9.3.3 Unknown dose** | | | | | | | | |
| Findling 2006 | 2.3 | 2.7386 | 120 | 4.6 | 2.7478 | 39 | 18.7% | -0.84 [-1.21, -0.46] |
| **Subtotal (95% CI)** | | | **120** | | | **39** | **18.7%** | **-0.84 [-1.21, -0.46]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 4.39 (P < 0.0001) | | | | | | | | |
| **Total (95% CI)** | | | **407** | | | **289** | **100.0%** | **-0.85 [-1.02, -0.69]** |
| Heterogeneity: Tau² = 0.00; Chi² = 1.63, df = 5 (P = 0.90); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 10.39 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.66, df = 2 (P = 0.72), I² = 0% | | | | | | | | |



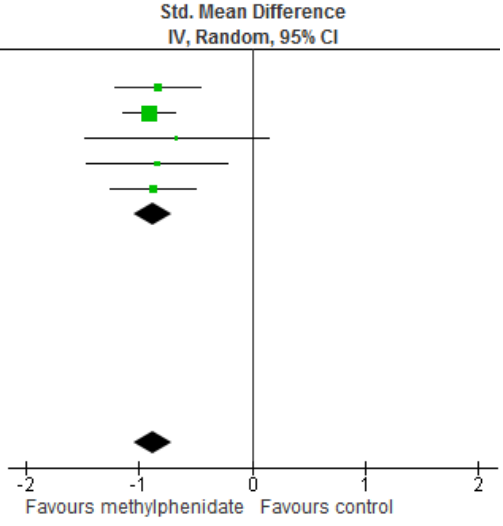

**9.4 Subgroup analysis: duration of treatment**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **9.4.1 Short term (up to 6 months)** | | | | | | | | |
| Findling 2006 | 2.3 | 2.7386 | 120 | 4.6 | 2.7478 | 39 | 19.6% | -0.84 [-1.21, -0.46] |
| Greenhill 2002 | 4.9 | 4.66 | 155 | 10.3 | 6.92 | 159 | 50.3% | -0.91 [-1.14, -0.68] |
| Ialongo 1994 | 3.07 | 2.78 | 13 | 5.83 | 5 | 12 | 4.1% | -0.67 [-1.48, 0.14] |
| Van der Meere 1999a | 37.8 | 5.8543 | 22 | 42.8 | 5.8543 | 21 | 6.9% | -0.84 [-1.46, -0.21] |
| Wolraich 2001 | 1.78 | 2.99 | 81 | 5.21 | 5.12 | 46 | 19.0% | -0.88 [-1.25, -0.50] |
| **Subtotal (95% CI)** | | | **391** | | | **277** | **100.0%** | **-0.87 [-1.04, -0.71]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 4 (P = 0.98); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 10.39 (P < 0.00001) | | | | | | | | |
| **9.4.2 Long term (over 6 months)** | | | | | | | | |
| **Subtotal (95% CI)** | | | **0** | | | **0** | | **Not estimable** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | | |
| **Total (95% CI)** | | | **391** | | | **277** | **100.0%** | **-0.87 [-1.04, -0.71]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 4 (P = 0.98); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 10.39 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | |



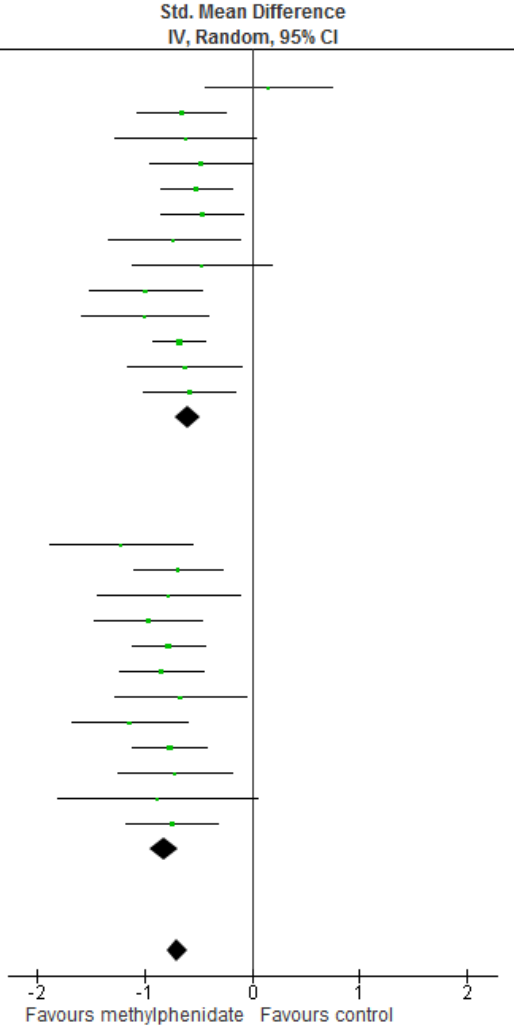

**9.5 Subgroup analysis: parallel-group trials versus first-period cross-over trials**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **9.5.1 Parallel-group trials** | | | | | | | | |
| Findling 2006 | 2.3 | 2.7386 | 120 | 4.6 | 2.7478 | 39 | 19.6% | -0.84 [-1.21, -0.46] |
| Greenhill 2002 | 4.9 | 4.66 | 155 | 10.3 | 6.92 | 159 | 50.3% | -0.91 [-1.14, -0.68] |
| Ialongo 1994 | 3.07 | 2.78 | 13 | 5.83 | 5 | 12 | 4.1% | -0.67 [-1.48, 0.14] |
| Van der Meere 1999a | 37.8 | 5.8543 | 22 | 42.8 | 5.8543 | 21 | 6.9% | -0.84 [-1.46, -0.21] |
| Wolraich 2001 | 1.78 | 2.99 | 81 | 5.21 | 5.12 | 46 | 19.0% | -0.88 [-1.25, -0.50] |
| **Subtotal (95% CI)** | | | **391** | | | **277** | **100.0%** | **-0.87 [-1.04, -0.71]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 4 (P = 0.98); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 10.39 (P < 0.00001) | | | | | | | | |
| **9.5.2 First-period cross-over trials** | | | | | | | | |
| **Subtotal (95% CI)** | | | **0** | | | **0** | | **Not estimable** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | | |
| **Total (95% CI)** | | | **391** | | | **277** | **100.0%** | **-0.87 [-1.04, -0.71]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 4 (P = 0.98); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 10.39 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | |



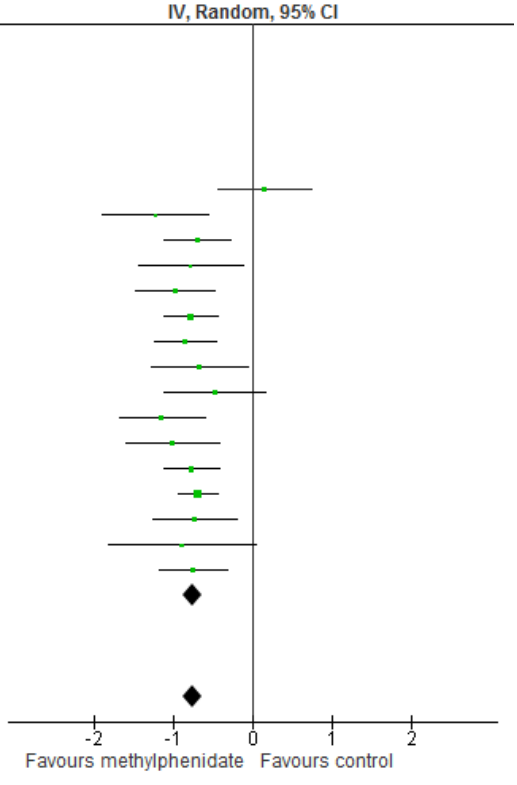
**9.6 General behaviour, cross-over trials (endpoint data)**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **9.6.1 Low dose** | | | | | | | | |
| Brown 1991 | 0.44 | 0.7 | 22 | 0.35 | 0.42 | 22 | 2.3% | 0.15 [-0.44, 0.75] |
| Fabiano 2007 | 0.5 | 1.09 | 48 | 1.68 | 2.3 | 48 | 4.8% | -0.65 [-1.06, -0.24] |
| Fitzpatrick 1992a | 0.31 | 0.5 | 19 | 0.7 | 0.72 | 19 | 1.9% | -0.62 [-1.27, 0.04] |
| Gadow 1995 | 2.6 | 3.4 | 34 | 4.3 | 3.7 | 34 | 3.5% | -0.47 [-0.96, 0.01] |
| Gadow 2007 | 1.7 | 2.8 | 71 | 3.4 | 3.7 | 71 | 7.3% | -0.52 [-0.85, -0.18] |
| Gadow 2011 | 2.6 | 3 | 54 | 4.2 | 3.8 | 54 | 5.6% | -0.46 [-0.85, -0.08] |
| Kolko 1999 | 2.6 | 2.8 | 22 | 5.7 | 5.2 | 22 | 2.2% | -0.73 [-1.34, -0.12] |
| Lufi 2007 | 8.59 | 9.73 | 19 | 14 | 12.68 | 19 | 2.0% | -0.47 [-1.11, 0.18] |
| Pelham 1993a | 0.8 | 1.4 | 31 | 4 | 4.3 | 31 | 2.9% | -0.99 [-1.52, -0.46] |
| Pelham 1999 | 0.6 | 1 | 25 | 2.6 | 2.6 | 25 | 2.3% | -1.00 [-1.59, -0.41] |
| Pelham 2002 | 0.5 | 1.1 | 136 | 1.9 | 2.7 | 136 | 13.7% | -0.68 [-0.92, -0.43] |
| Pelham 2005 | 0.6 | 1.1 | 29 | 1.9 | 2.7 | 29 | 2.9% | -0.62 [-1.15, -0.09] |
| Smith 1998 | 0.9 | 1.8 | 45 | 2.5 | 3.4 | 45 | 4.6% | -0.58 [-1.01, -0.16] |
| **Subtotal (95% CI)** | | | **555** | | | **555** | **56.0%** | **-0.60 [-0.72, -0.48]** |
| Heterogeneity: Tau² = 0.00; Chi² = 11.82, df = 12 (P = 0.46); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 9.69 (P < 0.00001) | | | | | | | | |
| **9.6.2 High dose** | | | | | | | | |
| Chronis 2003 | 0.4 | 0.5 | 21 | 2.9 | 2.8 | 21 | 1.9% | -1.22 [-1.88, -0.56] |
| Fabiano 2007 | 0.4 | 1.22 | 48 | 1.68 | 2.3 | 48 | 4.8% | -0.69 [-1.10, -0.28] |
| Fitzpatrick 1992a | 0.26 | 0.31 | 19 | 0.7 | 0.72 | 19 | 1.9% | -0.78 [-1.44, -0.12] |
| Gadow 1995 | 1.4 | 2 | 34 | 4.3 | 3.7 | 34 | 3.2% | -0.96 [-1.47, -0.46] |
| Gadow 2007 | 1.1 | 1.9 | 71 | 3.4 | 3.7 | 71 | 7.0% | -0.78 [-1.12, -0.44] |
| Gadow 2011 | 1.6 | 2.1 | 54 | 4.2 | 3.8 | 54 | 5.3% | -0.84 [-1.24, -0.45] |
| Kolko 1999 | 2.7 | 3.5 | 22 | 5.7 | 5.2 | 22 | 2.2% | -0.66 [-1.27, -0.06] |
| Pelham 1993a | 0.4 | 1 | 31 | 4 | 4.3 | 31 | 2.8% | -1.14 [-1.68, -0.60] |
| Pelham 2001a | 1.99 | 3.03 | 68 | 5.09 | 4.85 | 68 | 6.7% | -0.76 [-1.11, -0.41] |
| Pelham 2005 | 0.4 | 1.1 | 29 | 1.9 | 2.7 | 29 | 2.9% | -0.72 [-1.25, -0.19] |
| Pelham 2011 | 4.7 | 4.3 | 10 | 9 | 5 | 10 | 0.9% | -0.88 [-1.81, 0.05] |
| Smith 1998 | 0.6 | 1.2 | 45 | 2.5 | 3.4 | 45 | 4.5% | -0.74 [-1.17, -0.31] |
| **Subtotal (95% CI)** | | | **452** | | | **452** | **44.0%** | **-0.82 [-0.95, -0.68]** |
| Heterogeneity: Tau² = 0.00; Chi² = 4.17, df = 11 (P = 0.96); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 11.76 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **1007** | | | **1007** | **100.0%** | **-0.69 [-0.78, -0.60]** |
| Heterogeneity: Tau² = 0.00; Chi² = 21.62, df = 24 (P = 0.60); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 15.05 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 5.63, df = 1 (P = 0.02), I² = 82.2% | | | | | | | | |



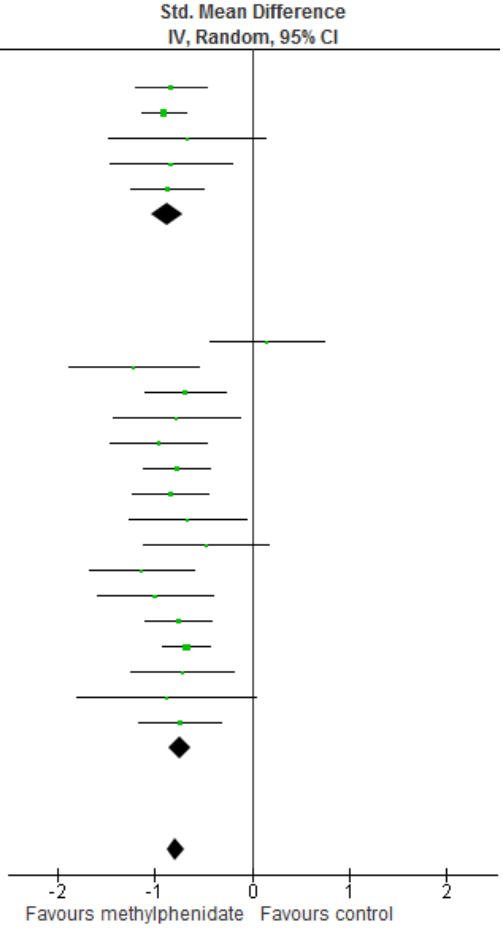

**9.7 Subgroup analysis: general behaviour, cross-over trials (endpoint data): risk of bias**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **9.7.1 Low risk of bias** | | | | | | | | |
| **Subtotal (95% CI)** | | | **0** | | | **0** | | **Not estimable** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | | |
| **9.7.2 High risk of bias** | | | | | | | | |
| Brown 1991 | 0.44 | 0.7 | 22 | 0.35 | 0.42 | 22 | 3.8% | 0.15 [-0.44, 0.75] |
| Chronis 2003 | 0.4 | 0.5 | 21 | 2.9 | 2.8 | 21 | 3.0% | -1.22 [-1.88, -0.56] |
| Fabiano 2007 | 0.4 | 1.22 | 48 | 1.68 | 2.3 | 48 | 7.6% | -0.69 [-1.10, -0.28] |
| Fitzpatrick 1992a | 0.26 | 0.31 | 19 | 0.7 | 0.72 | 19 | 3.1% | -0.78 [-1.44, -0.12] |
| Gadow 1995 | 1.4 | 2 | 34 | 4.3 | 3.7 | 34 | 5.2% | -0.96 [-1.47, -0.46] |
| Gadow 2007 | 1.1 | 1.9 | 71 | 3.4 | 3.7 | 71 | 10.8% | -0.78 [-1.12, -0.44] |
| Gadow 2011 | 1.6 | 2.1 | 54 | 4.2 | 3.8 | 54 | 8.3% | -0.84 [-1.24, -0.45] |
| Kolko 1999 | 2.7 | 3.5 | 22 | 5.7 | 5.2 | 22 | 3.6% | -0.66 [-1.27, -0.06] |
| Lufi 2007 | 8.59 | 9.73 | 19 | 14 | 12.68 | 19 | 3.2% | -0.47 [-1.11, 0.18] |
| Pelham 1993a | 0.4 | 1 | 31 | 4 | 4.3 | 31 | 4.6% | -1.14 [-1.68, -0.60] |
| Pelham 1999 | 0.6 | 1 | 25 | 2.6 | 2.6 | 25 | 3.8% | -1.00 [-1.59, -0.41] |
| Pelham 2001a | 1.99 | 3.03 | 68 | 5.09 | 4.85 | 68 | 10.4% | -0.76 [-1.11, -0.41] |
| Pelham 2002 | 0.5 | 1.1 | 136 | 1.9 | 2.7 | 136 | 19.4% | -0.68 [-0.92, -0.43] |
| Pelham 2005 | 0.4 | 1.1 | 29 | 1.9 | 2.7 | 29 | 4.7% | -0.72 [-1.25, -0.19] |
| Pelham 2011 | 4.7 | 4.3 | 10 | 9 | 5 | 10 | 1.6% | -0.88 [-1.81, 0.05] |
| Smith 1998 | 0.6 | 1.2 | 45 | 2.5 | 3.4 | 45 | 7.1% | -0.74 [-1.17, -0.31] |
| **Subtotal (95% CI)** | | | **654** | | | **654** | **100.0%** | **-0.75 [-0.87, -0.63]** |
| Heterogeneity: Tau² = 0.00; Chi² = 15.80, df = 15 (P = 0.40); I² = 5% | | | | | | | | |
| Test for overall effect: Z = 12.53 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **654** | | | **654** | **100.0%** | **-0.75 [-0.87, -0.63]** |
| Heterogeneity: Tau² = 0.00; Chi² = 15.80, df = 15 (P = 0.40); I² = 5% | | | | | | | | |
| Test for overall effect: Z = 12.53 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | |



**9.8 Subgroup analysis: all parallel-group trials and first-period cross-over trials (teacher-rated) versus cross-over trials (endpoint data)**

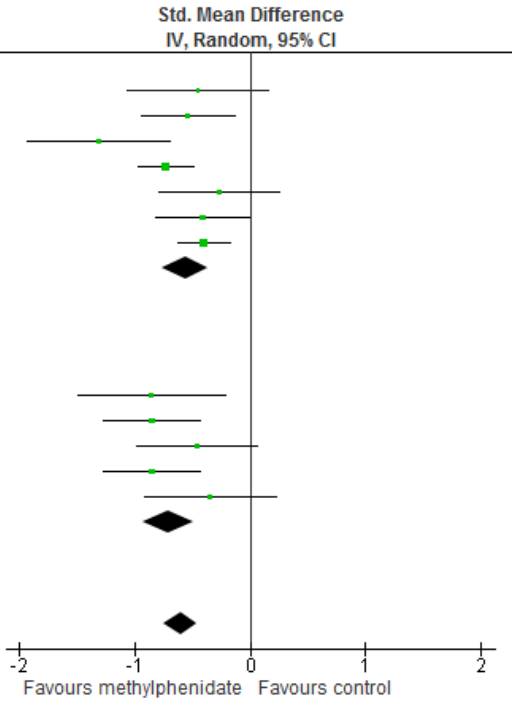
| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **9.8.1 All parallel-group trials and first-period cross-over trials** | | | | | | | | |
| Findling 2006 | 2.3 | 2.7386 | 120 | 4.6 | 2.7478 | 39 | 6.2% | -0.84 [-1.21, -0.46] |
| Greenhill 2002 | 4.9 | 4.66 | 155 | 10.3 | 6.92 | 159 | 16.0% | -0.91 [-1.14, -0.68] |
| Ialongo 1994 | 3.07 | 2.78 | 13 | 5.83 | 5 | 12 | 1.3% | -0.67 [-1.48, 0.14] |
| Van der Meere 1999a | 37.8 | 5.8543 | 22 | 42.8 | 5.8543 | 21 | 2.2% | -0.84 [-1.46, -0.21] |
| Wolraich 2001 | 1.78 | 2.99 | 81 | 5.21 | 5.12 | 46 | 6.1% | -0.88 [-1.25, -0.50] |
| **Subtotal (95% CI)** | | | **391** | | | **277** | **31.8%** | **-0.87 [-1.04, -0.71]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 4 (P = 0.98); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 10.39 (P < 0.00001) | | | | | | | | |
| **9.8.2 Cross-over trials (endpoint data)** | | | | | | | | |
| Brown 1991 | 0.44 | 0.7 | 22 | 0.35 | 0.42 | 22 | 2.5% | 0.15 [-0.44, 0.75] |
| Chronis 2003 | 0.4 | 0.5 | 21 | 2.9 | 2.8 | 21 | 2.0% | -1.22 [-1.88, -0.56] |
| Fabiano 2007 | 0.4 | 1.22 | 48 | 1.68 | 2.3 | 48 | 5.1% | -0.69 [-1.10, -0.28] |
| Fitzpatrick 1992a | 0.26 | 0.31 | 19 | 0.7 | 0.72 | 19 | 2.0% | -0.78 [-1.44, -0.12] |
| Gadow 1995 | 1.4 | 2 | 34 | 4.3 | 3.7 | 34 | 3.4% | -0.96 [-1.47, -0.46] |
| Gadow 2007 | 1.1 | 1.9 | 71 | 3.4 | 3.7 | 71 | 7.4% | -0.78 [-1.12, -0.44] |
| Gadow 2011 | 1.6 | 2.1 | 54 | 4.2 | 3.8 | 54 | 5.6% | -0.84 [-1.24, -0.45] |
| Kolko 1999 | 2.7 | 3.5 | 22 | 5.7 | 5.2 | 22 | 2.3% | -0.66 [-1.27, -0.06] |
| Lufi 2007 | 8.59 | 9.73 | 19 | 14 | 12.68 | 19 | 2.1% | -0.47 [-1.11, 0.18] |
| Pelham 1993a | 0.4 | 1 | 31 | 4 | 4.3 | 31 | 3.0% | -1.14 [-1.68, -0.60] |
| Pelham 1999 | 0.6 | 1 | 25 | 2.6 | 2.6 | 25 | 2.5% | -1.00 [-1.59, -0.41] |
| Pelham 2001a | 1.99 | 3.03 | 68 | 5.09 | 4.85 | 68 | 7.1% | -0.76 [-1.11, -0.41] |
| Pelham 2002 | 0.5 | 1.1 | 136 | 1.9 | 2.7 | 136 | 14.5% | -0.68 [-0.92, -0.43] |
| Pelham 2005 | 0.4 | 1.1 | 29 | 1.9 | 2.7 | 29 | 3.1% | -0.72 [-1.25, -0.19] |
| Pelham 2011 | 4.7 | 4.3 | 10 | 9 | 5 | 10 | 1.0% | -0.88 [-1.81, 0.05] |
| Smith 1998 | 0.6 | 1.2 | 45 | 2.5 | 3.4 | 45 | 4.7% | -0.74 [-1.17, -0.31] |
| **Subtotal (95% CI)** | | | **654** | | | **654** | **68.2%** | **-0.75 [-0.87, -0.63]** |
| Heterogeneity: Tau² = 0.00; Chi² = 15.80, df = 15 (P = 0.40); I² = 5% | | | | | | | | |
| Test for overall effect: Z = 12.53 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **1045** | | | **931** | **100.0%** | **-0.79 [-0.88, -0.70]** |
| Heterogeneity: Tau² = 0.00; Chi² = 17.73, df = 20 (P = 0.61); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 16.61 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 1.45, df = 1 (P = 0.23), I² = 31.1% | | | | | | | | |




## 10 - Independent assessor-rated general behaviour

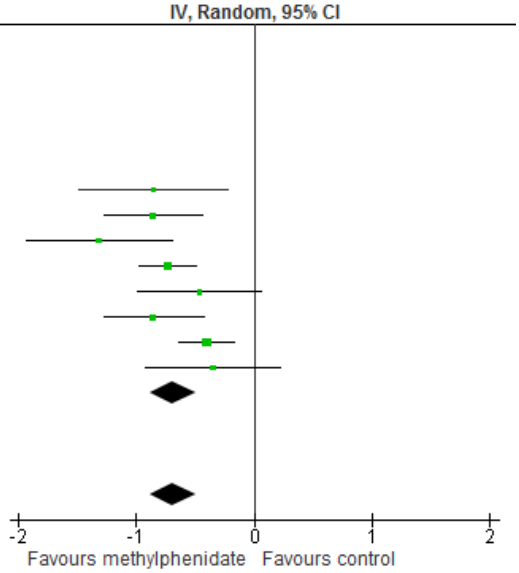
**10.1 General behaviour, cross-over trials (endpoint data)**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **10.1.1 Low dose** | | | | | | | | |
| Chronis 2003 | 3.1 | 2.4 | 21 | 4.4 | 3.2 | 21 | 4.8% | -0.45 [-1.06, 0.16] |
| Fabiano 2007 | 1.7 | 2.5 | 48 | 3.3 | 3.3 | 48 | 9.0% | -0.54 [-0.95, -0.13] |
| Pelham 1999 | 1.1 | 1.1 | 25 | 5.2 | 4.2 | 25 | 4.8% | -1.31 [-1.93, -0.70] |
| Pelham 2002 | 1.7 | 1.3 | 136 | 3.3 | 2.8 | 136 | 15.9% | -0.73 [-0.98, -0.49] |
| Pelham 2005 | 2.3 | 2.2 | 29 | 2.9 | 2.2 | 29 | 6.4% | -0.27 [-0.79, 0.25] |
| Pelham 2014 | 2.1 | 2.4 | 47 | 3.3 | 3.3 | 47 | 9.0% | -0.41 [-0.82, -0.00] |
| Schulz 2010 | 35.6 | 21 | 146 | 44.6 | 23.7 | 145 | 16.7% | -0.40 [-0.63, -0.17] |
| **Subtotal (95% CI)** | | | **452** | | | **451** | **66.5%** | **-0.56 [-0.76, -0.36]** |
| Heterogeneity: Tau² = 0.03; Chi² = 11.26, df = 6 (P = 0.08); I² = 47% | | | | | | | | |
| Test for overall effect: Z = 5.46 (P < 0.00001) | | | | | | | | |
| **10.1.2 High dose** | | | | | | | | |
| Chronis 2003 | 2.2 | 1.6 | 21 | 4.4 | 3.2 | 21 | 4.6% | -0.85 [-1.49, -0.22] |
| Fabiano 2007 | 1.1 | 1.5 | 48 | 3.3 | 3.3 | 48 | 8.7% | -0.85 [-1.27, -0.43] |
| Pelham 2005 | 2 | 1.6 | 29 | 2.9 | 2.2 | 29 | 6.3% | -0.46 [-0.98, 0.06] |
| Pelham 2014 | 1.1 | 1.5 | 47 | 3.3 | 3.3 | 47 | 8.5% | -0.85 [-1.27, -0.43] |
| Whalen 1990 | 3.25 | 4.81 | 24 | 4.79 | 3.9 | 24 | 5.4% | -0.35 [-0.92, 0.22] |
| **Subtotal (95% CI)** | | | **169** | | | **169** | **33.5%** | **-0.71 [-0.93, -0.49]** |
| Heterogeneity: Tau² = 0.00; Chi² = 3.50, df = 4 (P = 0.48); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 6.27 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **621** | | | **620** | **100.0%** | **-0.60 [-0.75, -0.46]** |
| Heterogeneity: Tau² = 0.02; Chi² = 16.14, df = 11 (P = 0.14); I² = 32% | | | | | | | | |
| Test for overall effect: Z = 7.99 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.92, df = 1 (P = 0.34), I² = 0% | | | | | | | | |



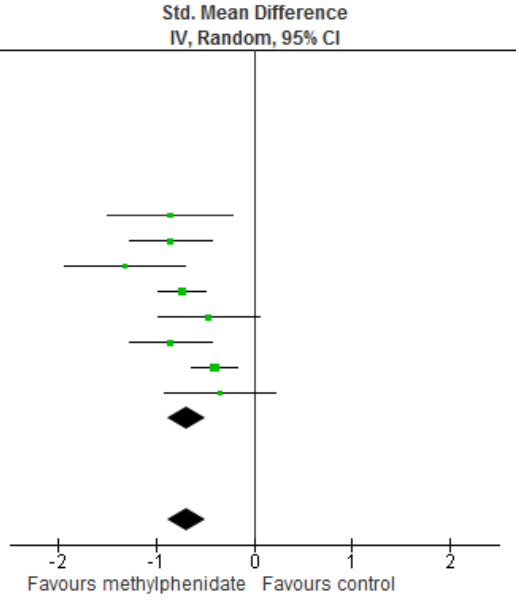
**10.2 Subgroup analysis: general behaviour, cross-over trials (endpoint data): risk of bias**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **10.2.1 Low risk of bias** | | | | | | | | |
| **Subtotal (95% CI)** | | | **0** | | | **0** | | **Not estimable** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | | |
| **10.2.2 High risk of bias** | | | | | | | | |
| Chronis 2003 | 2.2 | 1.6 | 21 | 4.4 | 3.2 | 21 | 7.3% | -0.85 [-1.49, -0.22] |
| Fabiano 2007 | 1.1 | 1.5 | 48 | 3.3 | 3.3 | 48 | 12.7% | -0.85 [-1.27, -0.43] |
| Pelham 1999 | 1.1 | 1.1 | 25 | 5.2 | 4.2 | 25 | 7.7% | -1.31 [-1.93, -0.70] |
| Pelham 2002 | 1.7 | 1.3 | 136 | 3.3 | 2.8 | 136 | 20.4% | -0.73 [-0.98, -0.49] |
| Pelham 2005 | 2 | 1.6 | 29 | 2.9 | 2.2 | 29 | 9.7% | -0.46 [-0.98, 0.06] |
| Pelham 2014 | 1.1 | 1.5 | 47 | 3.3 | 3.3 | 47 | 12.6% | -0.85 [-1.27, -0.43] |
| Schulz 2010 | 35.6 | 21 | 146 | 44.6 | 23.7 | 145 | 21.1% | -0.40 [-0.63, -0.17] |
| Whalen 1990 | 3.25 | 4.81 | 24 | 4.79 | 3.9 | 24 | 8.6% | -0.35 [-0.92, 0.22] |
| **Subtotal (95% CI)** | | | **476** | | | **475** | **100.0%** | **-0.69 [-0.88, -0.49]** |
| Heterogeneity: Tau² = 0.03; Chi² = 13.05, df = 7 (P = 0.07); I² = 46% | | | | | | | | |
| Test for overall effect: Z = 6.81 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **476** | | | **475** | **100.0%** | **-0.69 [-0.88, -0.49]** |
| Heterogeneity: Tau² = 0.03; Chi² = 13.05, df = 7 (P = 0.07); I² = 46% | | | | | | | | |
| Test for overall effect: Z = 6.81 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | |




**10.3 Subgroup analysis: all parallel-group trials and first-period cross-over trials (independent assessor-rated) compared with cross-over trials (endpoint**

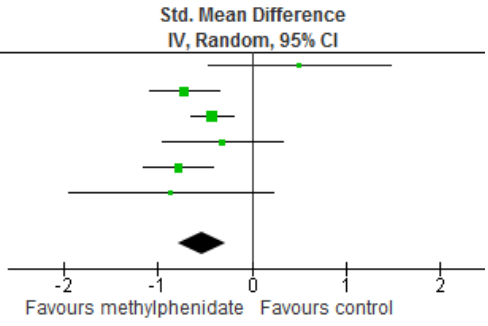
| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **10.3.1 Parallel-group trials and first-period cross-over trials** | | | | | | | | |
| **Subtotal (95% CI)** | | | **0** | | | **0** | | **Not estimable** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | | |
| **10.3.2 Cross-over trials (endpoint data)** | | | | | | | | |
| Chronis 2003 | 2.2 | 1.6 | 21 | 4.4 | 3.2 | 21 | 7.3% | -0.85 [-1.49, -0.22] |
| Fabiano 2007 | 1.1 | 1.5 | 48 | 3.3 | 3.3 | 48 | 12.7% | -0.85 [-1.27, -0.43] |
| Pelham 1999 | 1.1 | 1.1 | 25 | 5.2 | 4.2 | 25 | 7.7% | -1.31 [-1.93, -0.70] |
| Pelham 2002 | 1.7 | 1.3 | 136 | 3.3 | 2.8 | 136 | 20.4% | -0.73 [-0.98, -0.49] |
| Pelham 2005 | 2 | 1.6 | 29 | 2.9 | 2.2 | 29 | 9.7% | -0.46 [-0.98, 0.06] |
| Pelham 2014 | 1.1 | 1.5 | 47 | 3.3 | 3.3 | 47 | 12.6% | -0.85 [-1.27, -0.43] |
| Schulz 2010 | 35.6 | 21 | 146 | 44.6 | 23.7 | 145 | 21.1% | -0.40 [-0.63, -0.17] |
| Whalen 1990 | 3.25 | 4.81 | 24 | 4.79 | 3.9 | 24 | 8.6% | -0.35 [-0.92, 0.22] |
| **Subtotal (95% CI)** | | | **476** | | | **475** | **100.0%** | **-0.69 [-0.88, -0.49]** |
| Heterogeneity: Tau² = 0.03; Chi² = 13.05, df = 7 (P = 0.07); I² = 46% | | | | | | | | |
| Test for overall effect: Z = 6.81 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **476** | | | **475** | **100.0%** | **-0.69 [-0.88, -0.49]** |
| Heterogeneity: Tau² = 0.03; Chi² = 13.05, df = 7 (P = 0.07); I² = 46% | | | | | | | | |
| Test for overall effect: Z = 6.81 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | |




## 11 - Parent-rated general behaviour

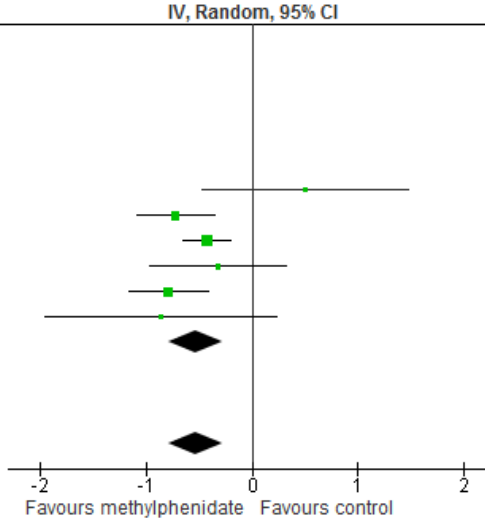
**11.1 All parallel-group trials and first-period cross-over trials**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Carlson 2007 | 1.9 | 9.4 | 9 | -2.1 | 4.8 | 8 | 5.9% | 0.50 [-0.47, 1.47] |
| Findling 2006 | 4.6 | 3.1768 | 120 | 6.9 | 3.1849 | 39 | 22.7% | -0.72 [-1.09, -0.35] |
| Greenhill 2002 | 7.4 | 5.9 | 155 | 10.1 | 6.7 | 159 | 32.8% | -0.43 [-0.65, -0.20] |
| Pliszka 2000 | 1.28 | 0.72 | 20 | 1.54 | 0.88 | 18 | 11.5% | -0.32 [-0.96, 0.32] |
| Wolraich 2001 | 4.81 | 3.87 | 81 | 8.09 | 4.63 | 46 | 22.4% | -0.78 [-1.16, -0.41] |
| Zeni 2009 | 0.9444 | 0.61798 | 9 | 1.6 | 0.85346 | 6 | 4.8% | -0.86 [-1.95, 0.23] |
| **Total (95% CI)** | | | **394** | | | **276** | **100.0%** | **-0.53 [-0.78, -0.27]** |
| Heterogeneity: Tau² = 0.04; Chi² = 8.67, df = 5 (P = 0.12); I² = 42% | | | | | | | | |
| Test for overall effect: Z = 4.09 (P < 0.0001) | | | | | | | | |



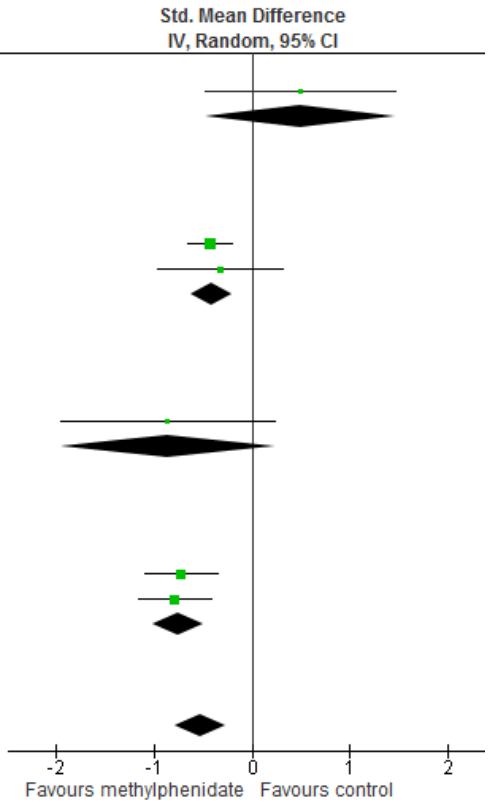
**11.2 Subgroup analysis: risk of bias**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **11.2.1 Low risk of bias** | | | | | | | | |
| **Subtotal (95% CI)** | | | **0** | | | **0** | | **Not estimable** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | | |
| **11.2.2 High risk of bias** | | | | | | | | |
| Carlson 2007 | 1.9 | 9.4 | 9 | -2.1 | 4.8 | 8 | 5.9% | 0.50 [-0.47, 1.47] |
| Findling 2006 | 4.6 | 3.1768 | 120 | 6.9 | 3.1849 | 39 | 22.7% | -0.72 [-1.09, -0.35] |
| Greenhill 2002 | 7.4 | 5.9 | 155 | 10.1 | 6.7 | 159 | 32.8% | -0.43 [-0.65, -0.20] |
| Pliszka 2000 | 1.28 | 0.72 | 20 | 1.54 | 0.88 | 18 | 11.5% | -0.32 [-0.96, 0.32] |
| Wolraich 2001 | 4.81 | 3.87 | 81 | 8.09 | 4.63 | 46 | 22.4% | -0.78 [-1.16, -0.41] |
| Zeni 2009 | 0.9444 | 0.61798 | 9 | 1.6 | 0.85346 | 6 | 4.8% | -0.86 [-1.95, 0.23] |
| **Subtotal (95% CI)** | | | **394** | | | **276** | **100.0%** | **-0.53 [-0.78, -0.27]** |
| Heterogeneity: Tau² = 0.04; Chi² = 8.67, df = 5 (P = 0.12); I² = 42% | | | | | | | | |
| Test for overall effect: Z = 4.09 (P < 0.0001) | | | | | | | | |
| **Total (95% CI)** | | | **394** | | | **276** | **100.0%** | **-0.53 [-0.78, -0.27]** |
| Heterogeneity: Tau² = 0.04; Chi² = 8.67, df = 5 (P = 0.12); I² = 42% | | | | | | | | |
| Test for overall effect: Z = 4.09 (P < 0.0001) | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | |



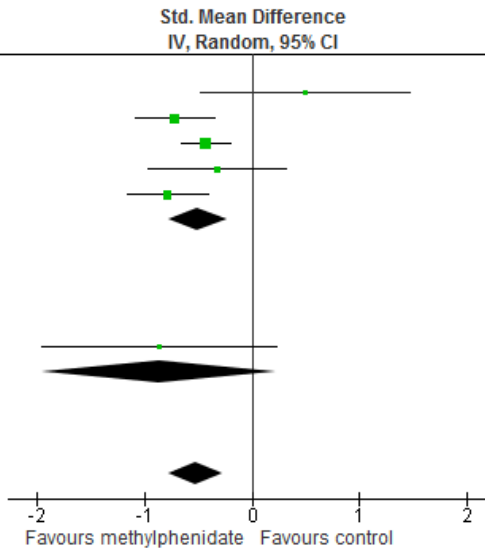

**11.3 Subgroup analysis: types of scales**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **11.3.1 The Weekly Parent Ratings of Evening and Morning Behaviour (WPREMB) - Revised** | | | | | | | | |
| Carlson 2007 | 1.9 | 9.4 | 9 | -2.1 | 4.8 | 8 | 5.9% | 0.50 [-0.47, 1.47] |
| **Subtotal (95% CI)** | | | **9** | | | **8** | **5.9%** | **0.50 [-0.47, 1.47]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 1.01 (P = 0.31) | | | | | | | | |
| **11.3.2 Conners' Global Index (CGI) - Parent** | | | | | | | | |
| Greenhill 2002 | 7.4 | 5.9 | 155 | 10.1 | 6.7 | 159 | 32.8% | -0.43 [-0.65, -0.20] |
| Pliszka 2000 | 1.28 | 0.72 | 20 | 1.54 | 0.88 | 18 | 11.5% | -0.32 [-0.96, 0.32] |
| **Subtotal (95% CI)** | | | **175** | | | **177** | **44.3%** | **-0.41 [-0.63, -0.20]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.76); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 3.85 (P = 0.0001) | | | | | | | | |
| **11.3.3 Swanson, Nolan and Pelham, Fourth Edition - Oppositional (SNAP-IV-Oppositional)** | | | | | | | | |
| Zeni 2009 | 0.9444 | 0.61798 | 9 | 1.6 | 0.85346 | 6 | 4.8% | -0.86 [-1.95, 0.23] |
| **Subtotal (95% CI)** | | | **9** | | | **6** | **4.8%** | **-0.86 [-1.95, 0.23]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 1.54 (P = 0.12) | | | | | | | | |
| **11.3.4 IOWA Conners' Rating Scale - Oppositional/Defiant (IOWA-I/O)** | | | | | | | | |
| Findling 2006 | 4.6 | 3.1768 | 120 | 6.9 | 3.1849 | 39 | 22.7% | -0.72 [-1.09, -0.35] |
| Wolraich 2001 | 4.81 | 3.87 | 81 | 8.09 | 4.63 | 46 | 22.4% | -0.78 [-1.16, -0.41] |
| **Subtotal (95% CI)** | | | **201** | | | **85** | **45.1%** | **-0.75 [-1.01, -0.49]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 5.59 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **394** | | | **276** | **100.0%** | **-0.53 [-0.78, -0.27]** |
| Heterogeneity: Tau² = 0.04; Chi² = 8.67, df = 5 (P = 0.12); I² = 42% | | | | | | | | |
| Test for overall effect: Z = 4.09 (P < 0.0001) | | | | | | | | |
| Test for subgroup differences: Chi² = 8.52, df = 3 (P = 0.04), I² = 64.8% | | | | | | | | |



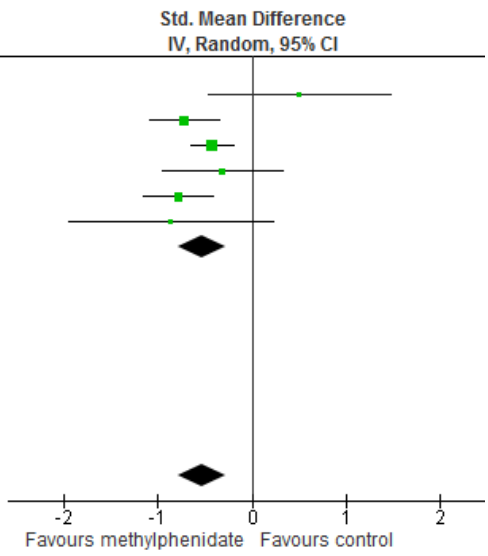
**11.4 Subgroup analysis: parallel-group trials compared with first-period cross-over trials**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **11.4.1 Parallel-group trials** | | | | | | | | |
| Carlson 2007 | 1.9 | 9.4 | 9 | -2.1 | 4.8 | 8 | 5.9% | 0.50 [-0.47, 1.47] |
| Findling 2006 | 4.6 | 3.1768 | 120 | 6.9 | 3.1849 | 39 | 22.7% | -0.72 [-1.09, -0.35] |
| Greenhill 2002 | 7.4 | 5.9 | 155 | 10.1 | 6.7 | 159 | 32.8% | -0.43 [-0.65, -0.20] |
| Pliszka 2000 | 1.28 | 0.72 | 20 | 1.54 | 0.88 | 18 | 11.5% | -0.32 [-0.96, 0.32] |
| Wolraich 2001 | 4.81 | 3.87 | 81 | 8.09 | 4.63 | 46 | 22.4% | -0.78 [-1.16, -0.41] |
| **Subtotal (95% CI)** | | | 385 | | | 270 | 95.2% | **-0.51 [-0.78, -0.23]** |
| Heterogeneity: Tau² = 0.05; Chi² = 8.30, df = 4 (P = 0.08); I² = 52% | | | | | | | | |
| Test for overall effect: Z = 3.62 (P = 0.0003) | | | | | | | | |
| **11.4.2 First-period cross-over trials** | | | | | | | | |
| Zeni 2009 | 0.9444 | 0.61798 | 9 | 1.6 | 0.85346 | 6 | 4.8% | -0.86 [-1.95, 0.23] |
| **Subtotal (95% CI)** | | | 9 | | | 6 | 4.8% | **-0.86 [-1.95, 0.23]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 1.54 (P = 0.12) | | | | | | | | |
| **Total (95% CI)** | | | 394 | | | 276 | 100.0% | **-0.53 [-0.78, -0.27]** |
| Heterogeneity: Tau² = 0.04; Chi² = 8.67, df = 5 (P = 0.12); I² = 42% | | | | | | | | |
| Test for overall effect: Z = 4.09 (P < 0.0001) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.38, df = 1 (P = 0.54), I² = 0% | | | | | | | | |



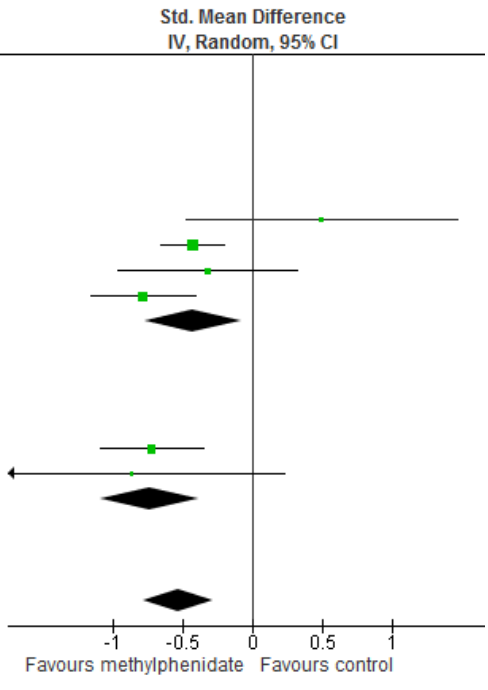

**11.5 Subgroup analysis: duration of treatment**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **11.5.1 Short term (up to 6 months)** | | | | | | | | |
| Carlson 2007 | 1.9 | 9.4 | 9 | -2.1 | 4.8 | 8 | 5.9% | 0.50 [-0.47, 1.47] |
| Findling 2006 | 4.6 | 3.1768 | 120 | 6.9 | 3.1849 | 39 | 22.7% | -0.72 [-1.09, -0.35] |
| Greenhill 2002 | 7.4 | 5.9 | 155 | 10.1 | 6.7 | 159 | 32.8% | -0.43 [-0.65, -0.20] |
| Pliszka 2000 | 1.28 | 0.72 | 20 | 1.54 | 0.88 | 18 | 11.5% | -0.32 [-0.96, 0.32] |
| Wolraich 2001 | 4.81 | 3.87 | 81 | 8.09 | 4.63 | 46 | 22.4% | -0.78 [-1.16, -0.41] |
| Zeni 2009 | 0.9444 | 0.61798 | 9 | 1.6 | 0.85346 | 6 | 4.8% | -0.86 [-1.95, 0.23] |
| **Subtotal (95% CI)** | | | 394 | | | 276 | 100.0% | **-0.53 [-0.78, -0.27]** |
| Heterogeneity: Tau² = 0.04; Chi² = 8.67, df = 5 (P = 0.12); I² = 42% | | | | | | | | |
| Test for overall effect: Z = 4.09 (P < 0.0001) | | | | | | | | |
| **11.5.2 Long term (over 6 months)** | | | | | | | | |
| **Subtotal (95% CI)** | | | 0 | | | 0 | | **Not estimable** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | | |
| **Total (95% CI)** | | | 394 | | | 276 | 100.0% | **-0.53 [-0.78, -0.27]** |
| Heterogeneity: Tau² = 0.04; Chi² = 8.67, df = 5 (P = 0.12); I² = 42% | | | | | | | | |
| Test for overall effect: Z = 4.09 (P < 0.0001) | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | |



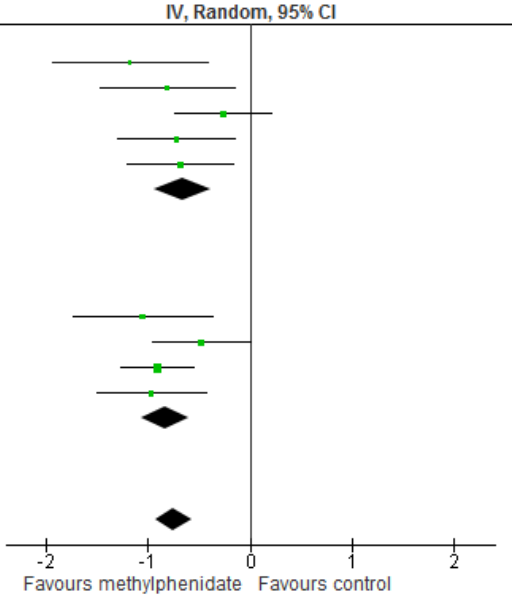

**11.6 Subgroup analysis: dose**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **11.6.1 Low dose** | | | | | | | | |
| **Subtotal (95% CI)** | | | 0 | | | 0 | | **Not estimable** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | | |
| **11.6.2 High dose** | | | | | | | | |
| Carlson 2007 | 1.9 | 9.4 | 9 | -2.1 | 4.8 | 8 | 5.9% | 0.50 [-0.47, 1.47] |
| Greenhill 2002 | 7.4 | 5.9 | 155 | 10.1 | 6.7 | 159 | 32.8% | -0.43 [-0.65, -0.20] |
| Pliszka 2000 | 1.28 | 0.72 | 20 | 1.54 | 0.88 | 18 | 11.5% | -0.32 [-0.96, 0.32] |
| Wolraich 2001 | 4.81 | 3.87 | 81 | 8.09 | 4.63 | 46 | 22.4% | -0.78 [-1.16, -0.41] |
| **Subtotal (95% CI)** | | | 265 | | | 231 | 72.6% | **-0.42 [-0.77, -0.08]** |
| Heterogeneity: Tau² = 0.06; Chi² = 6.88, df = 3 (P = 0.08); I² = 56% | | | | | | | | |
| Test for overall effect: Z = 2.39 (P = 0.02) | | | | | | | | |
| **11.6.3 Unknown dose** | | | | | | | | |
| Findling 2006 | 4.6 | 3.1768 | 120 | 6.9 | 3.1849 | 39 | 22.7% | -0.72 [-1.09, -0.35] |
| Zeni 2009 | 0.9444 | 0.61798 | 9 | 1.6 | 0.85346 | 6 | 4.8% | -0.86 [-1.95, 0.23] |
| **Subtotal (95% CI)** | | | 129 | | | 45 | 27.4% | **-0.73 [-1.08, -0.38]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 4.11 (P < 0.0001) | | | | | | | | |
| **Total (95% CI)** | | | 394 | | | 276 | 100.0% | **-0.53 [-0.78, -0.27]** |
| Heterogeneity: Tau² = 0.04; Chi² = 8.67, df = 5 (P = 0.12); I² = 42% | | | | | | | | |
| Test for overall effect: Z = 4.09 (P < 0.0001) | | | | | | | | |
| Test for subgroup differences: Chi² = 1.52, df = 1 (P = 0.22), I² = 34.3% | | | | | | | | |



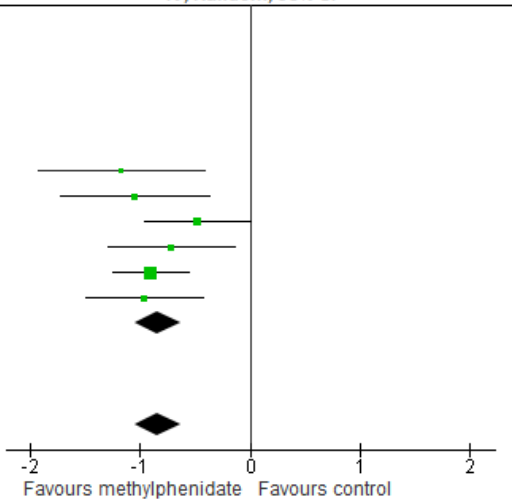
**11.7 General behaviour, cross-over trials (endpoint data)**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Placebo Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **11.7.1 Low dose** | | | | | | | | |
| Findling 2007 | 56 | 8 | 16 | 73.9 | 19.4 | 16 | 5.5% | -1.18 [-1.93, -0.42] |
| Fitzpatrick 1992a | 0.68 | 0.53 | 19 | 1.15 | 0.61 | 19 | 7.2% | -0.81 [-1.47, -0.14] |
| Gadow 1995 | 1.9 | 1.7 | 34 | 2.4 | 2 | 34 | 13.3% | -0.27 [-0.74, 0.21] |
| Pelham 1999 | 1.2 | 1.4 | 25 | 2.5 | 2.1 | 25 | 9.5% | -0.72 [-1.29, -0.14] |
| Pelham 2005 | 1.3 | 1.1 | 30 | 2.5 | 2.2 | 30 | 11.3% | -0.68 [-1.20, -0.16] |
| **Subtotal (95% CI)** | | | **124** | | | **124** | **46.7%** | **-0.65 [-0.93, -0.38]** |
| Heterogeneity: Tau² = 0.01; Chi² = 4.60, df = 4 (P = 0.33); I² = 13% | | | | | | | | |
| Test for overall effect: Z = 4.61 (P < 0.00001) | | | | | | | | |
| **11.7.2 High dose** | | | | | | | | |
| Fitzpatrick 1992a | 0.6 | 0.39 | 19 | 1.15 | 0.61 | 19 | 6.8% | -1.05 [-1.73, -0.37] |
| Gadow 1995 | 1.5 | 1.7 | 34 | 2.4 | 2 | 34 | 13.0% | -0.48 [-0.96, 0.00] |
| Pelham 2001a | 5.26 | 3.85 | 68 | 8.85 | 4.04 | 68 | 22.8% | -0.90 [-1.26, -0.55] |
| Pelham 2005 | 0.8 | 1.1 | 30 | 2.5 | 2.2 | 30 | 10.7% | -0.96 [-1.50, -0.43] |
| **Subtotal (95% CI)** | | | **151** | | | **151** | **53.3%** | **-0.83 [-1.07, -0.60]** |
| Heterogeneity: Tau² = 0.00; Chi² = 2.85, df = 3 (P = 0.42); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 6.90 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **275** | | | **275** | **100.0%** | **-0.75 [-0.93, -0.56]** |
| Heterogeneity: Tau² = 0.01; Chi² = 8.57, df = 8 (P = 0.38); I² = 7% | | | | | | | | |
| Test for overall effect: Z = 8.05 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.91, df = 1 (P = 0.34), I² = 0% | | | | | | | | |



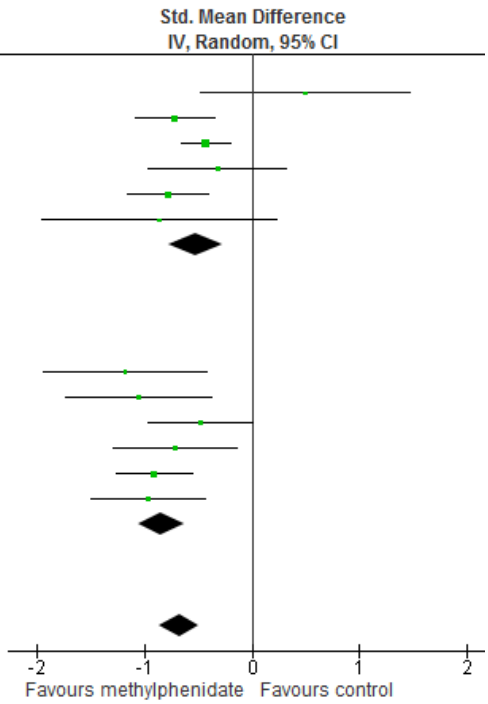

**11.8 Subgroup analysis: general behaviour, cross-over trials (endpoint data): risk of bias**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **11.8.1 Low risk of bias** | | | | | | | | |
| **Subtotal (95% CI)** | | | **0** | | | **0** | | **Not estimable** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | | |
| **11.8.2 High risk of bias** | | | | | | | | |
| Findling 2007 | 56 | 8 | 16 | 73.9 | 19.4 | 16 | 7.7% | -1.18 [-1.93, -0.42] |
| Fitzpatrick 1992a | 0.6 | 0.39 | 19 | 1.15 | 0.61 | 19 | 9.4% | -1.05 [-1.73, -0.37] |
| Gadow 1995 | 1.5 | 1.7 | 34 | 2.4 | 2 | 34 | 18.9% | -0.48 [-0.96, 0.00] |
| Pelham 1999 | 1.2 | 1.4 | 25 | 2.5 | 2.1 | 25 | 13.4% | -0.72 [-1.29, -0.14] |
| Pelham 2001a | 5.26 | 3.85 | 68 | 8.85 | 4.04 | 68 | 35.3% | -0.90 [-1.26, -0.55] |
| Pelham 2005 | 0.8 | 1.1 | 30 | 2.5 | 2.2 | 30 | 15.3% | -0.96 [-1.50, -0.43] |
| **Subtotal (95% CI)** | | | **192** | | | **192** | **100.0%** | **-0.84 [-1.05, -0.63]** |
| Heterogeneity: Tau² = 0.00; Chi² = 3.78, df = 5 (P = 0.58); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 7.87 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **192** | | | **192** | **100.0%** | **-0.84 [-1.05, -0.63]** |
| Heterogeneity: Tau² = 0.00; Chi² = 3.78, df = 5 (P = 0.58); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 7.87 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | |



**11.9 Subgroup analysis: all parallel-group trials and first-period cross-over trials (parent-rated) compared with cross-over trials (endpoint data)**

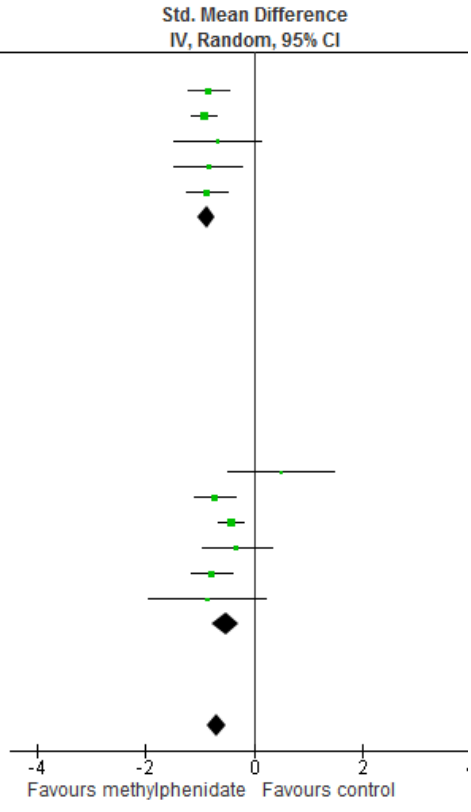
| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **11.9.1 All parallel-group trials and first-period cross-over trials** | | | | | | | | |
| Carlson 2007 | 1.9 | 9.4 | 9 | -2.1 | 4.8 | 8 | 3.1% | 0.50 [-0.47, 1.47] |
| Findling 2006 | 4.6 | 3.1768 | 120 | 6.9 | 3.1849 | 39 | 12.1% | -0.72 [-1.09, -0.35] |
| Greenhill 2002 | 7.4 | 5.9 | 155 | 10.1 | 6.7 | 159 | 17.7% | -0.43 [-0.65, -0.20] |
| Pliszka 2000 | 1.28 | 0.72 | 20 | 1.54 | 0.88 | 18 | 6.0% | -0.32 [-0.96, 0.32] |
| Wolraich 2001 | 4.81 | 3.87 | 81 | 8.09 | 4.63 | 46 | 11.9% | -0.78 [-1.16, -0.41] |
| Zeni 2009 | 0.9444 | 0.61798 | 9 | 1.6 | 0.85346 | 6 | 2.5% | -0.86 [-1.95, 0.23] |
| **Subtotal (95% CI)** | | | **394** | | | **276** | **53.3%** | **-0.53 [-0.78, -0.27]** |
| Heterogeneity: Tau² = 0.04; Chi² = 8.67, df = 5 (P = 0.12); I² = 42% | | | | | | | | |
| Test for overall effect: Z = 4.09 (P < 0.0001) | | | | | | | | |
| **11.9.2 Cross-over trials (endpoint data)** | | | | | | | | |
| Findling 2007 | 56 | 8 | 16 | 73.9 | 19.4 | 16 | 4.7% | -1.18 [-1.93, -0.42] |
| Fitzpatrick 1992a | 0.6 | 0.39 | 19 | 1.15 | 0.61 | 19 | 5.5% | -1.05 [-1.73, -0.37] |
| Gadow 1995 | 1.5 | 1.7 | 34 | 2.4 | 2 | 34 | 9.0% | -0.48 [-0.96, 0.00] |
| Pelham 1999 | 1.2 | 1.4 | 25 | 2.5 | 2.1 | 25 | 7.1% | -0.72 [-1.29, -0.14] |
| Pelham 2001a | 5.26 | 3.85 | 68 | 8.85 | 4.04 | 68 | 12.7% | -0.90 [-1.26, -0.55] |
| Pelham 2005 | 0.8 | 1.1 | 30 | 2.5 | 2.2 | 30 | 7.8% | -0.96 [-1.50, -0.43] |
| **Subtotal (95% CI)** | | | **192** | | | **192** | **46.7%** | **-0.84 [-1.05, -0.63]** |
| Heterogeneity: Tau² = 0.00; Chi² = 3.78, df = 5 (P = 0.58); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 7.87 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **586** | | | **468** | **100.0%** | **-0.68 [-0.86, -0.50]** |
| Heterogeneity: Tau² = 0.04; Chi² = 18.02, df = 11 (P = 0.08); I² = 39% | | | | | | | | |
| Test for overall effect: Z = 7.30 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 3.56, df = 1 (P = 0.06), I² = 71.9% | | | | | | | | |




## 12 - Additional subgroup analyses of general behaviour: parallel-group trials and first-period cross-over trials

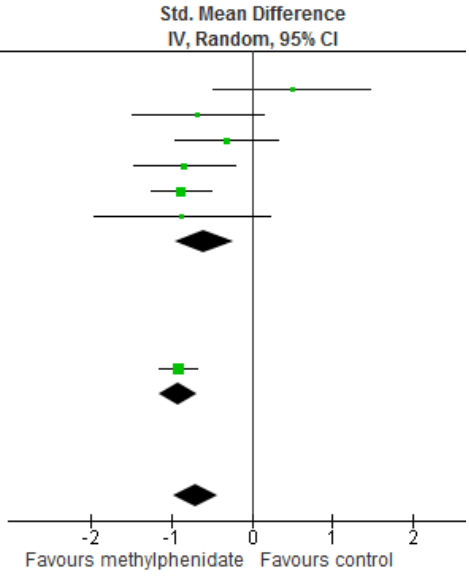
**12.1 Comparisions of raters**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **12.1.1 Teacher-rated** | | | | | | | | |
| Findling 2006 | 2.3 | 2.7386 | 120 | 4.6 | 2.7478 | 39 | 11.4% | -0.84 [-1.21, -0.46] |
| Greenhill 2002 | 4.9 | 4.66 | 155 | 10.3 | 6.92 | 159 | 16.8% | -0.91 [-1.14, -0.68] |
| Ialongo 1994 | 3.07 | 2.78 | 13 | 5.83 | 5 | 12 | 3.9% | -0.67 [-1.48, 0.14] |
| Van der Meere 1999a | 37.8 | 5.8543 | 22 | 42.8 | 5.8543 | 21 | 5.8% | -0.84 [-1.46, -0.21] |
| Wolraich 2001 | 1.78 | 2.99 | 81 | 5.21 | 5.12 | 46 | 11.3% | -0.88 [-1.25, -0.50] |
| **Subtotal (95% CI)** | | | **391** | | | **277** | **49.2%** | **-0.87 [-1.04, -0.71]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 4 (P = 0.98); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 10.39 (P < 0.00001) | | | | | | | | |
| **12.1.2 Independent assessor-rated** | | | | | | | | |
| **Subtotal (95% CI)** | | | **0** | | | **0** | | **Not estimable** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | | |
| **12.1.3 Parent-rated** | | | | | | | | |
| Carlson 2007 | 1.9 | 9.4 | 9 | -2.1 | 4.8 | 8 | 2.8% | 0.50 [-0.47, 1.47] |
| Findling 2006 | 4.6 | 3.1768 | 120 | 6.9 | 3.1849 | 39 | 11.5% | -0.72 [-1.09, -0.35] |
| Greenhill 2002 | 7.4 | 5.9 | 155 | 10.1 | 6.7 | 159 | 17.2% | -0.43 [-0.65, -0.20] |
| Pliszka 2000 | 1.28 | 0.72 | 20 | 1.54 | 0.88 | 18 | 5.6% | -0.32 [-0.96, 0.32] |
| Wolraich 2001 | 4.81 | 3.87 | 81 | 8.09 | 4.63 | 46 | 11.4% | -0.78 [-1.16, -0.41] |
| Zeni 2009 | 0.9444 | 0.61798 | 9 | 1.6 | 0.85346 | 6 | 2.3% | -0.86 [-1.95, 0.23] |
| **Subtotal (95% CI)** | | | **394** | | | **276** | **50.8%** | **-0.53 [-0.78, -0.27]** |
| Heterogeneity: Tau² = 0.04; Chi² = 8.67, df = 5 (P = 0.12); I² = 42% | | | | | | | | |
| Test for overall effect: Z = 4.09 (P < 0.0001) | | | | | | | | |
| **Total (95% CI)** | | | **785** | | | **553** | **100.0%** | **-0.69 [-0.86, -0.52]** |
| Heterogeneity: Tau² = 0.03; Chi² = 17.93, df = 10 (P = 0.06); I² = 44% | | | | | | | | |
| Test for overall effect: Z = 7.77 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 5.10, df = 1 (P = 0.02), I² = 80.4% | | | | | | | | |



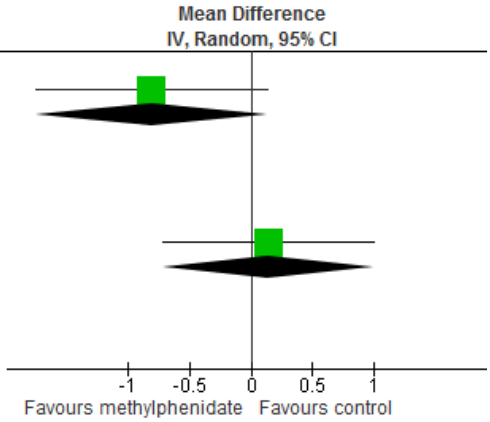
12.2 Comorbidity versus no comorbidity

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **12.2.1 ADHD with comorbidity** | | | | | | | | |
| Carlson 2007 | 1.9 | 9.4 | 9 | -2.1 | 4.8 | 8 | 6.7% | 0.50 [-0.47, 1.47] |
| Ialongo 1994 | 3.07 | 2.78 | 13 | 5.83 | 5 | 12 | 8.9% | -0.67 [-1.48, 0.14] |
| Pliszka 2000 | 1.28 | 0.72 | 20 | 1.54 | 0.88 | 18 | 12.6% | -0.32 [-0.96, 0.32] |
| Van der Meere 1999a | 37.8 | 5.8543 | 22 | 42.8 | 5.8543 | 21 | 13.0% | -0.84 [-1.46, -0.21] |
| Wolraich 2001 | 1.78 | 2.99 | 81 | 5.21 | 5.12 | 46 | 22.6% | -0.88 [-1.25, -0.50] |
| Zeni 2009 | 0.9444 | 0.61798 | 9 | 1.6 | 0.85346 | 6 | 5.5% | -0.86 [-1.95, 0.23] |
| **Subtotal (95% CI)** | | | **154** | | | **111** | **69.2%** | **-0.59 [-0.95, -0.23]** |
| Heterogeneity: Tau² = 0.08; Chi² = 8.25, df = 5 (P = 0.14); I² = 39% | | | | | | | | |
| Test for overall effect: Z = 3.23 (P = 0.001) | | | | | | | | |
| **12.2.2 ADHD without comorbidity** | | | | | | | | |
| Greenhill 2002 | 4.9 | 4.66 | 155 | 10.3 | 6.92 | 159 | 30.8% | -0.91 [-1.14, -0.68] |
| **Subtotal (95% CI)** | | | **155** | | | **159** | **30.8%** | **-0.91 [-1.14, -0.68]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 7.68 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **309** | | | **270** | **100.0%** | **-0.70 [-0.98, -0.43]** |
| Heterogeneity: Tau² = 0.05; Chi² = 10.19, df = 6 (P = 0.12); I² = 41% | | | | | | | | |
| Test for overall effect: Z = 4.99 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 2.13, df = 1 (P = 0.14), I² = 53.0% | | | | | | | | |

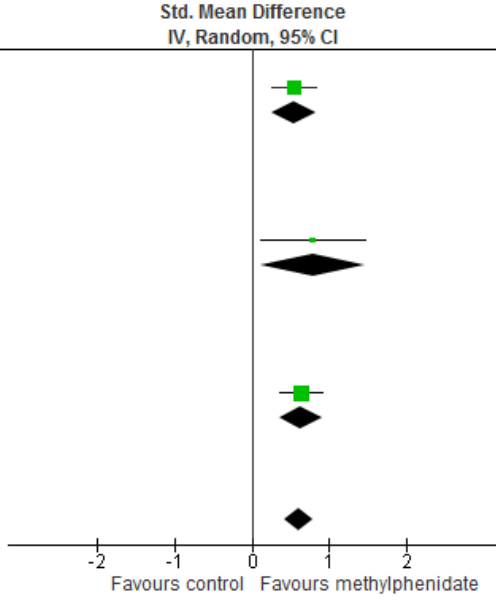



12.3 Cross-over trials: first-period data versus endpoint data (teacher-, parent-, and independent assessor-rated)

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **12.3.1 First-period data** | | | | | | | | |
| Zeni 2009 | 0.8911 | 0.72428 | 9 | 1.7 | 1.0996 | 7 | 100.0% | -0.81 [-1.75, 0.13] |
| **Subtotal (95% CI)** | | | **9** | | | **7** | **100.0%** | **-0.81 [-1.75, 0.13]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 1.68 (P = 0.09) | | | | | | | | |
| **12.3.2 Endpoint data** | | | | | | | | |
| Zeni 2009 | 1.06 | 0.78442 | 6 | 0.9188 | 0.83766 | 8 | 100.0% | 0.14 [-0.71, 1.00] |
| **Subtotal (95% CI)** | | | **6** | | | **8** | **100.0%** | **0.14 [-0.71, 1.00]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.32 (P = 0.75) | | | | | | | | |
| Test for subgroup differences: Chi² = 2.14, df = 1 (P = 0.14), I² = 53.3% | | | | | | | | |




## 13 - Quality of life: parallel-group trials and first-period cross-over trials

13.1 Subgroup analysis: types of scales

| Study or Subgroup | Methylphenidate Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **13.1.1 Child Health Questionnaire (CHQ)** | | | | | | | | |
| Newcorn 2008 | 7.8 | 12.7 | 193 | 1 | 12 | 64 | 43.5% | 0.54 [0.25, 0.83] |
| **Subtotal (95% CI)** | | | **193** | | | **64** | **43.5%** | **0.54 [0.25, 0.83]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 3.70 (P = 0.0002) | | | | | | | | |
| **13.1.2 Children´s Global Assessment Scale (CGAS)** | | | | | | | | |
| Szobot 2004 | 69.1 | 11.3 | 19 | 59.7 | 12.1 | 17 | 7.7% | 0.79 [0.10, 1.47] |
| **Subtotal (95% CI)** | | | **19** | | | **17** | **7.7%** | **0.79 [0.10, 1.47]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 2.26 (P = 0.02) | | | | | | | | |
| **13.1.3 Child Health and Illness Profile, Child Edition: Parent Report Form (CHIP-CE:PRF)** | | | | | | | | |
| Coghill 2013 | 7.1 | 11.5892 | 111 | -0.2 | 11.2223 | 110 | 48.8% | 0.64 [0.37, 0.91] |
| **Subtotal (95% CI)** | | | **111** | | | **110** | **48.8%** | **0.64 [0.37, 0.91]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 4.62 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **323** | | | **191** | **100.0%** | **0.61 [0.42, 0.80]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.52, df = 2 (P = 0.77); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 6.30 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.52, df = 2 (P = 0.77), I² = 0% | | | | | | | | |