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Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults (Review)

Epstein T, Patsopoulos NA, Weiser M

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TABLE OF CONTENTS

[Intervention Review]

Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults

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ABSTRACT

Background

Symptoms of attention deficit hyperactivity disorder (ADHD), diagnosed mainly in children, often persist into adulthood. Adults in this group have a high rate of other psychiatric problems and functional difficulties in a number of key areas such as academic achievement, interpersonal relationships, and employment. Although the usefulness of immediate-release methylphenidate in children has been extensively studied, studies in adults, which are few, demonstrate varying results.

Objectives

To evaluate the efficacy and tolerability of immediate-release methylphenidate versus placebo in the treatment of adults with ADHD.

Search methods

We searched the following databases in November 2013: CENTRAL, Ovid MEDLINE, EMBASE, PsycINFO, Database of Abstracts of Reviews of Effects (DARE), and two trials registers. Biosis was searched in December 2013. We inspected references of all relevant papers to identify more studies and contacted authors of recently published trials.

Selection criteria

We included all randomized trials comparing immediate-release methylphenidate versus placebo in participants aged 18 years or older with ADHD. We excluded trials conducted on subpopulations of adults with ADHD such as adults with both ADHD and substance dependence.

Data collection and analysis

Two review authors independently selected trials, extracted data, and assessed trial risk of bias. We contacted authors of trials to ask for additional and missing data. For dichotomous outcomes, we calculated risk ratios (RRs) and 95% confidence intervals (CIs). For continuous outcomes, we calculated mean differences (MDs) or standardized mean differences (SMDs) with 95% CIs.

Main results

Results from the 11 randomized controlled trials (474 participants, counting participants from cross-over studies as a single arm, and counting both arms from parallel studies) included in the review demonstrated improvement in core clinical ADHD symptoms of hyperactivity, impulsivity, and inattentiveness, and overall improvement. We were able to pool results from 10 studies, which included 466 participants.

Most included studies were judged to have unclear risk of bias for most categories. However, as all studies were randomized, double-blind, and placebo-controlled and, in general, did not contain factors that significantly decreased the quality of the body of evidence, the quality of evidence was assessed as "high" for most outcomes according to the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) approach. For one outcome-inattentiveness-most information came from studies at unclear risk of bias, and so the quality of evidence for this outcome was judged as "moderate."

Results are given as SMD for each of the core clinical symptoms of ADHD. In all cases, participant numbers were calculated by counting participants in a single arm from cross-over studies and in both arms from parallel studies. The SMD for the outcome of hyperactivity was -0.60 (95% CI -1.11 to -0.09, 6 studies, number of participants (n) = 245, high-quality evidence) in favor of immediate-release methylphenidate; the SMD for impulsivity was -0.62 (95% CI -1.08 to -0.17, 5 studies, n = 207, high-quality evidence) in favor of immediate-release methylphenidate; and the SMD for inattentiveness was -0.66 (95% CI -1.02 to -0.30, 7 studies, n = 391, moderate-quality evidence) in favor of immediate-release methylphenidate. Moderate to extreme statistical heterogeneity was detected for all outcomes. Subgroup analysis comparing high versus low doses did not indicate that higher doses of immediate-release methylphenidate were associated with greater efficacy.

For overall change, the SMD was -0.72 (95% CI -1.12 to -0.32, 9 studies, n = 455, high-quality evidence) in favor of immediate-release methylphenidate.

The effects of immediate-release methylphenidate on anxiety and depression as parameters of general changes in mental state were equivocal. Some trials reported reduction in depression and anxiety, others detailed no change, and still others described an increase in depressive and anxious symptoms.

The most common adverse effect was loss of appetite, in some cases with weight loss. Although no study reported either of these effects as problematic or severe, the included studies were of short duration; thus clinical significance could not be properly assessed. Five studies reported changes in systolic or diastolic blood pressure, and three reported increases in heart rate. None of these results were judged to present cause for concern. No study reported clinically significant adverse effects-cardiovascular or other. Three studies did not mention adverse effects. We were unable to determine whether adverse effects were not discussed by study authors because none occurred, or because no data on adverse effects were collected.

Authors' conclusions

Data from randomized controlled trials suggest that immediate-release methylphenidate is efficacious for treating adults with ADHD with symptoms of hyperactivity, impulsivity, and inattentiveness, and for improving their overall clinical condition. Trial data suggest that adverse effects from immediate-release methylphenidate for adults with ADHD are not of serious clinical significance, although this conclusion may be limited, certainly in the case of weight loss, by the short duration of published studies.

PLAIN LANGUAGE SUMMARY

Ritalin for adult attention deficit hyperactivity disorder (ADHD)

Background

Symptoms of attention deficit hyperactivity disorder (ADHD), diagnosed mainly in children, often persist into adulthood, afflicting 1% to 6% of the general population. Adults with ADHD have higher rates of other psychiatric problems and functional difficulties in a number of key areas such as academic achievement, interpersonal relationships, employment, and driving performance.

Although the usefulness of immediate-release methylphenidate (known by its trademark name Ritalin) in children has been studied extensively, the same does not hold true for adults, for whom few studies have yielded mixed results. We therefore wanted to examine whether Ritalin is effective and safe for the treatment of adults with ADHD.

Methods

To find all relevant studies, we searched eight electronic databases, including the Cochrane Central Register of Controlled Studies (CENTRAL), MEDLINE, and Clinicaltrials.gov, to look for reports published in all languages in July 2009, June 2011, and October 2012, and between November 2013 and December 2013. We inspected reference lists of all relevant studies for additional studies and contacted authors of recently published trials. We included all studies when participants were adults with ADHD who were randomly allocated to receive the active drug or a placebo ("dummy") pill. We did not include studies conducted on specific subgroups of adults with ADHD, such as adults with both ADHD and substance dependence.

Key results

This review was based on 11 included studies with a total of 474 participants. We combined the results of 10 of these studies, which included 466 participants, and found that immediate-release methylphenidate was effective when compared with placebo for the core symptoms of ADHD-hyperactivity, impulsivity, and inattentiveness. Treatment with immediate-release methylphenidate also improved the overall clinical condition. Whether treatment with immediate-release methylphenidate is helpful for anxiety or depression remains unclear, as results were mixed.

The main side effect reported was a decrease in appetite, in some cases with weight loss. No serious side effects were noted. However, studies were of short duration, and it was unclear whether weight loss may have become a serious issue over time. Although five studies reported a rise in blood pressure and others described a rise in heart rate, these side effects were infrequent or were not of major clinical significance. It was unclear whether the three studies that did not mention adverse effects found none or had set out with the intent to measure them.

Quality of the evidence

Overall, the body of evidence about use of methylphenidate in adults with ADHD is of high quality. It shows that methylphenidate improves ADHD symptoms in adults and suggests that side effects are not serious.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults

Patient or population: adults with attention deficit hyperactivity disorder (ADHD)
Settings: North America and the Netherlands
Intervention: immediate-release methylphenidate

Outcomes	Illustrative comparative risks* (95% CI) Corresponding risk Immediate-release methylphenidate	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
Hyperactivity Follow-up: 2 to 3 weeks	Mean hyperactivity in the intervention groups was **0.6 standard deviations lower** (1.11 to 0.09 lower)	245 (6 studies)	⊕⊕⊕⊕ **high**	All 6 studies reporting this outcome were cross-over studies. Therefore, the actual number of participants is 245
Impulsivity Follow-up: 2 to 3 weeks	Mean impulsivity in the intervention groups was **0.62 standard deviations lower** (1.08 to 0.17 lower)	207 (5 studies)	⊕⊕⊕⊕ **high**	All 5 studies reporting this outcome were cross-over studies. Therefore, the actual number of participants is 207
Inattentiveness Follow-up: 2 to 6 weeks	Mean inattentiveness in the intervention groups was **0.66 standard deviations lower** (1.02 to 0.30 lower)	391 (7)	⊕⊕⊕ **moderate**	6 of the studies reporting this outcome were cross-over studies, and 1 was a parallel study. The actual number of participants is 245 for the cross-over studies plus 104 in the experimental group and 42 in the placebo group, adding up to 391 participants. Quality rating was downgraded as most information was derived from studies at unclear risk of bias

Overall change Follow-up: 2 to 7 weeks	Mean overall change in the intervention groups was **0.72 standard deviations lower** (1.12 to 0.32 lower)	455 (9 studies)	⊕⊕⊕⊕ **high**	7 of the studies reporting this outcome were cross-over studies, and 2 were parallel studies. The actual number of participants is 290 from the cross-over studies, plus, in the experimental group from the 2 parallel studies, 104 and 8 participants, respectively, and 42 and 11 participants respectively. in the placebo group from the 2 parallel studies, totaling 455 participants

CI: confidence interval.

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.

BACKGROUND

Description of the condition

Attention deficit hyperactivity disorder (ADHD) is one of the most commonly diagnosed and treated psychiatric disorders in children. Epidemiological studies have reported that between 3% and 7% of children in the United States, New Zealand and/or Australia, Germany, and Brazil suffer from ADHD (Szatmari 1992; APA 2000; Willcutt 2012). Data from the child and adolescent component of the Australian National Survey of Mental Health and Well-being suggest that the prevalence of ADHD among children could be as high as 11% (Sawyer 2001). The Great Smoky Mountain Study, conducted in North Carolina, USA, in 1996, assessed children nine, 11, and 13 years old, and diagnosed hyperactivity in 1.9% (Costello 1996); a more recent published study conducted in the USA reported that the prevalence of ADHD among eight- to 15-year-old children is 8.7% (Froehlich 2007). Another review found the pooled prevalence of ADHD in children aged 18 years or younger to be 5.29% (Polanczyk 2007). It is very likely that rates of ADHD are similar in most countries, with variations in prevalence probably due to different diagnostic criteria and different means of case ascertainment (Faraone 2003). Prospective longitudinal follow-up studies have reported that symptoms of ADHD persist into adulthood at rates varying from 4% to 60% (Mannuzza 1993; Biederman 1996; Hechtman 1999). Studies suggest that between one-third and two-thirds of children diagnosed with ADHD continue to manifest symptoms of ADHD as adults (Wender 2001a). Although persistence of the complete syndrome is relatively rare, persistence of individual symptoms, particularly impaired attention, is quite common (Faraone 2000). It is now estimated that the prevalence of ADHD in the general adult population is 3% to 4% (Fayyad 2007; Spencer 2008).
Clinical manifestations of ADHD vary, and children and adults may present differently. The main clinical features, as the name implies, include disturbed attention and impulsive or hyperactive

behavior or both. Major persistent features of ADHD in adults involve difficulty sustaining, focusing, or shifting attention. People with ADHD, therefore, are easily distracted and often act impulsively.

Data from cross-sectional, retrospective, and follow-up studies indicate that children and youths with ADHD are at risk of developing other psychiatric difficulties in childhood, adolescence, and adulthood, including antisocial behavior and mood, anxiety, and substance use disorders (Biederman 1991). Among adults with ADHD, Borland 1976 reported high rates of antisocial personality, anxiety, and depressive disorders, as well as substance misuse, but these studies were limited in that they did not control for comorbid conduct disorder in childhood (Fergusson 1993). Biederman 1994 reported that adults with ADHD had significantly higher lifetime rates of major depression, oppositional disorder, drug dependence, agoraphobia, and social phobia. In addition, studies suggest that adults with ADHD suffer from functional impairments. Murphy 1996 and Barkley 2002 reported that, compared with controls without ADHD, adults with ADHD had greater numbers of speeding violations and suspended driving licenses, changed jobs more frequently, performed worse at work, were more likely to have resigned or been fired from their jobs, and were more likely to have had multiple marriages (Murphy 1996). Barkley 1996 evaluated driving skills and negative driving outcomes of older teens and young adults with ADHD compared with control participants. Young adults with ADHD had greater numbers of speeding citations, suspended licenses, and traffic accidents, including those causing bodily injury. In another study, college students with ADHD had lower mean grade point averages, were more likely to have been on academic probation, and had greater numbers of academic problems in comparison with the general student population (Heiligenstein 1999).

Description of the intervention

Stimulants, specifically methylphenidate and dexamphetamine derivatives, tricyclic antidepressants (Wender 1990; Wilens 1995), atomoxetine (Faraone 2008), and antihypertensives, such as beta-blockers (Mattes 1986), are the medications used to treat individuals with ADHD. Stimulants in general, and methylphenidate in particular, are considered to be first-line interventions in ADHD. Methylphenidate can be administered in a slow-release form, but this review focuses on immediate-release methylphenidate, commonly known by its trademark name, Ritalin.

How the intervention might work

Methylphenidate is a centrally acting dopamine agonist. It blocks dopamine transporters and the return of dopamine into presynaptic nerve endings, thereby increasing dopamine concentration in the synapse. It is postulated that methylphenidate promotes release of stored dopamine from presynaptic vesicles (Volkow 2001; Volkow 2005; Engert 2008). However, the precise mechanism of action of methylphenidate is unknown as yet.

Although the mechanism of action of methylphenidate is not fully understood at this time, several theories as to its therapeutic effect have been proposed.

It may be that the effect of methylphenidate is due in part to the magnitude of dopamine increases induced by stimuli that by themselves generate weak responses. Methylphenidate-induced increases in dopamine, a neurotransmitter involved in motivation and reward, could enhance the salience of the task and the interest and attention it elicits, thus improving performance (Volkow 2005).

Therapeutic doses of methylphenidate elevate tonic dopamine while inhibiting phasic transmitter release in subcortical structures, leading to reduced postsynaptic receptor stimulation and psychomotor activation in response to salient stimuli. Animal studies have shown, however, that when administered at doses producing clinically relevant drug plasma levels and enhancing cognitive function, methylphenidate preferentially activates dopamine and noradrenaline efflux within the prefrontal cortex relative to subcortical structures (Engert 2008).

The actions of methylphenidate may also be mediated by stimulation of the noradrenergic alpha2-receptor. Changes in catecholaminergic tone clinically manifest as improvements in attention deficit, distractibility, and motor hyperactivity in people with ADHD (Wilens 2008).

In the text of this review, we used only the term "methylphenidate," which is the name of the active ingredient in preparations sold under different brand names. We included only studies using the immediate-release form of methylphenidate.

Why it is important to do this review

Many clinical trials (Findling 2008) document the efficacy of stimulants in the treatment of ADHD in the child and adolescent population, and several systematic reviews (Miller 1998; Jadad 1999; Brown 2005) indicate that stimulant medications are efficacious in the treatment of children and adolescents with ADHD. In contrast to the large volume of data on stimulants in children and adolescents diagnosed with ADHD, far fewer studies have examined the use of stimulants in adult ADHD, and trials assessing the efficacy of treatment with immediate-release methylphenidate in adults with ADHD have shown inconsistent results. Although Kuperman 2001 found no significant difference between placebo and immediate-release methylphenidate, Spencer 1995 reported a large and significant difference in efficacy (78% for immediate-release methylphenidate as opposed to 4% for placebo). The clinical reality is challenging, as ADHD in adults is widespread with many people needing treatment, but most clinical trials have used relatively small sample sizes and have reported inconsistent results. Hence, a systematic review carried out within the rigor-

ous methodological framework of The Cochrane Collaboration provides an important and reliable summary of current evidence relevant for clinical practice.

Previous systematic reviews of immediate-release methylphenidate in adults with ADHD also reported inconsistent results. Faraone 2004 performed a meta-analysis assessing the influence of study design features on medication effects. Six trials were included, with 140 adults with ADHD receiving methylphenidate and 113 receiving placebo. The mean effect size of 0.9 was statistically significant. Larger methylphenidate effect sizes were associated with physician ratings of outcome and use of higher doses. When treatment was optimized to high doses, the effect size for methylphenidate in adults was 1.3.

Koesters 2009, on the other hand, included 16 studies in a meta-analysis with an overall effect size of d = 0.42-only half the effect reported in Faraone's meta-analysis (Faraone 2004). In this study, subgroup analyses were conducted with respect to parallel-group versus cross-over design and self versus observer ratings. The relationship between dose and effect size was explored by weighted regression analysis.

These two reviews used different statistical methodology, present significantly different effect sizes, and convey different clinical implications; thus the present review contributes to what is still an apparently unanswered question.

OBJECTIVES

To evaluate the efficacy and tolerability of immediate-release methylphenidate versus placebo in the treatment of adults with ADHD.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials.

Types of participants

Adults diagnosed with ADHD. Studies dealing exclusively with specific subpopulations of adults with ADHD, such as those with a comorbidity of substance abuse disorder or brain injury, were excluded from this review. This exclusion criterion represents a post hoc protocol change for this review (see Differences between protocol and review). This change was made because inclusion of such studies would obfuscate the clinical relevance of this review.

Types of interventions

- Immediate-release methylphenidate administered at any dosage as part of any treatment regimen.
- Placebo or no intervention.

Types of outcome measures

Primary outcomes

Symptoms of ADHD

Changes in hyperactivity, impulsivity, and inattentiveness as symptoms of ADHD measured by any clinical scale.

Secondary outcomes

Overall change

The number of people per treatment group who showed an overall change in condition.

General mental state changes

Changes in measures of depression, anxiety, or other psychiatric symptoms. Assessments of functioning.

Adverse effects

Any adverse effects, including worsening of symptoms (defined as any deleterious changes in the symptoms of ADHD on any scale).

Search methods for identification of studies

We ran the searches in July 2009, June 2011, and October 2012. The most recent searches were run between 27 November 2013, and 12 December 2013. We did not limit by date, language or by publication type.

Electronic searches

We searched the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 10).
- Ovid MEDLINE, 1946 to November Week 2 2013.
- Ovid MEDLINE In-Process and Other Non-Indexed Citations.
- EMBASE (Ovid), 1980 to Week 47 2013.
- PsycINFO (Ovid), 1806 to November Week 3 2013.
- Biosis (Web of Science), January 1990 to December 2013.
- Database of Abstracts of Reviews of Effects (DARE) (2013, Issue 4).
- ClinicalTrials.gov (clinicaltrials.gov/).
- International Clinical Trials Registry Platform (apps.who.int/trialsearch/).

See Appendix 1 for search strategies.

Searching other resources

Reference searching

We searched the reference lists of potentially relevant papers to find additional studies.

Personal contact

We contacted the first author of each included study for unpublished data or for information about other relevant studies. We received responses from the authors of Tenenbaum 2002, Kooij 2004, and Wender 2011.

Data collection and analysis

Selection of studies

TE and MW independently inspected every report identified by the search to determine whether the study was likely to be relevant. This was done on the basis of title, or abstract when available or when the title was not clear. Disagreements were resolved by discussion. When this was not possible, the full article was obtained and was inspected by the review authors, again independently, to assess its relevance to this review. In the event that disagreements were not resolved by discussion, the article was added to those awaiting assessment, and the authors of the study were contacted for clarification of ambiguous or missing descriptions of the methodology (specifically, randomization and allocation concealment). The review authors documented justification for excluding studies from the review.

Data extraction and management

Data were independently extracted by TE and MW. When disputes arose, they were resolved by discussion. Outcomes were assessed using continuous measures (eg, changes on a behavior scale) or dichotomous measures (eg, "no important changes" or "important changes" in a person's behavior).

Assessment of risk of bias in included studies

TE and MW independently assessed risk of bias of trials fulfilling the review inclusion criteria.

For each individual study, the following information was extracted and assessed as having "high," "low," or "unclear" risk of bias.

- Randomization-Was assignment to treatment groups truly random, and by what methods was the participant sequence generated?
- Allocation concealment-Was allocation adequately concealed?
- Blinding-Were participants and those assessing outcomes blinded to treatment allocation?
- Incomplete data-Were participants excluded from participation in the study after random assignment, and how were these data treated? Was the analysis conducted on an intent-to-treat basis? (How complete was follow-up? How were outcomes considered for people who withdrew? Were they included in the analysis?)
- Selective reporting-Were results given for all outcomes that the study reported were assessed?
- Risk of bias from other sources-Were any other biases identified in the study?

Unit of analysis issues

When cross-over trials were encountered, we evaluated whether the cross-over design was suitable. If suitable, we extracted all necessary data to calculate effect sizes of paired analyses.

Specifically, for continuous outcomes, we calculated correlation coefficients between the two treatment groups from available data (eg, paired *t* test) and then estimated the standardized mean difference (SMD) and respective standard error (SE) (Curtin 2002b). If correlation coefficients were negative, we treated the respective cross-over trials as parallel (Higgins 2008). When data for determining the correlation between the two arms were unavailable for specific outcomes in cross-over trials, we used correlation coefficients from other cross-over studies or different outcomes of the same study, based on methodological criteria. When taking correlation coefficients from other studies, we used studies providing the same dosage regimen. When taking correlation coefficients from different outcomes of the same study, we used the outcomes that were most similar according to clinical significance. In cases for which no external information was available, we treated cross-over trials as parallel.

When the outcome was binary, we tried (in studies using a cross-over design) to identify information per treatment group and per sequence period. When this information was unavailable, we analyzed these as parallel trials (Curtin 2002a). The latter approach can give rise to a unit of analysis error, leading to a more conservative analysis (Higgins 2008; Section 16.4.5).

Assessment of heterogeneity

Consistency of results was assessed visually and by examination of I^2 (Higgins 2003), a measure that describes the percentage of total variation across studies that is due to heterogeneity rather than to the play of chance (Higgins 2003). The values of I^2 lie between 0% and 100%, and a simplified categorization of heterogeneity could be low, moderate, or high based on I^2 values of 25%, 50%, or 75%, respectively (Higgins 2003). Furthermore, we used Cochran's Q test of homogeneity to test for statistical heterogeneity.

For most outcomes, we observed evidence of high statistical heterogeneity ($I^2 > 75\%$), probably reflecting clinical or methodolog-

ical diversity, or both, among studies. However, the decision to refrain from synthesizing data-in light of the high level of heterogeneity-may have led to "vote counting," which is advised against in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). Because a small number of studies, most of which included a small number of participants, were identified, we chose to synthesize results using a random-effects meta-analysis model. Effect sizes given for each outcome indicate the average intervention effect along with pooled estimates and confidence intervals referring to the center of the distribution of intervention effects. The range of intervention effects observed in these studies may be thought to provide a rough idea of the spread of the distribution of true intervention effects, but, in fact, this range will be slightly too wide, as it also describes the random error in observed effect estimates (Higgins 2008). We discussed the limitations this poses when explaining the results in the Discussion section.

Although we decided to synthesize these studies using a random-effects model, the small number of studies per outcome (n < 10) did not allow investigation of the source of heterogeneity with methods such as meta-regression (Higgins 2008).

Data synthesis

Before synthesizing the data, we decided that the most important factor in the decision of whether different scales should be synthesized was their clinical homogeneity. Therefore, we opted to synthesize all clinically homogenous scales. When both validated and nonvalidated scales were presented in the same study for the same outcome, we reported the validated scales. When both physician-rated and non-physician-rated scales (whether validated or not) were reported for the same outcome in the same study (eg, Kooij 2004, for the outcome of general change in condition), we used physician-rated scales. We chose to synthesize self-rated and physician-rated scales and validated and nonvalidated scales that were clinically homogenous across different studies if not doing so would have prevented synthesis of study data.

To clarify these choices, we present several tables in the Additional tables section. Table 1 lists the different scales used by each study for each type of outcome.

- Continuous data: For continuous outcomes, mean difference (MD) between groups was estimated when the same scales were used. When different scales were used to measure the same outcome, standardized mean difference (SMD) was used.
- Binary data: We used effect size and respective standard error (SE) as reported; in the absence of these, we perused data from available tables to estimate the odds ratio (OR) and the SE (Higgins 2008). To accommodate overall synthesis when an outcome had both binary and continuous data, we transformed binary data to SMD and respective SE (Higgins 2008; Section 9.4.6). In addition to the overall synthesis, we performed separate meta-analyses per subgroup.
- Endpoint versus change data: When possible, endpoint data were presented; if both endpoint and change data were available for the same outcome, only the former were reported in this review.

When possible, we entered data in such a way that the area to the left of the line of no effect indicated a favorable outcome for methylphenidate.

Subgroup analysis and investigation of heterogeneity

Results were stratified according to low dosage (0 to 0.9 mg/kg/d) and high dosage (more than 0.9 mg/kg/d).

GRADE

Outcomes used to populate Summary of findings for the main comparison included the primary outcomes of hyperactivity, impulsivity, and inattentiveness (ie, the main clinical characteristics of ADHD) and the secondary outcome of overall change (ie, a general indication of the effect of an intervention).

We used the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach to rate the quality of evidence on the outcomes included in Summary of findings for the main comparison. Through this approach, randomized controlled trials are downgraded from high to moderate to low or very low quality of evidence on the basis of the following five factors (Higgins 2011): limitations in design and implementation, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of results, and high probability of publication bias.

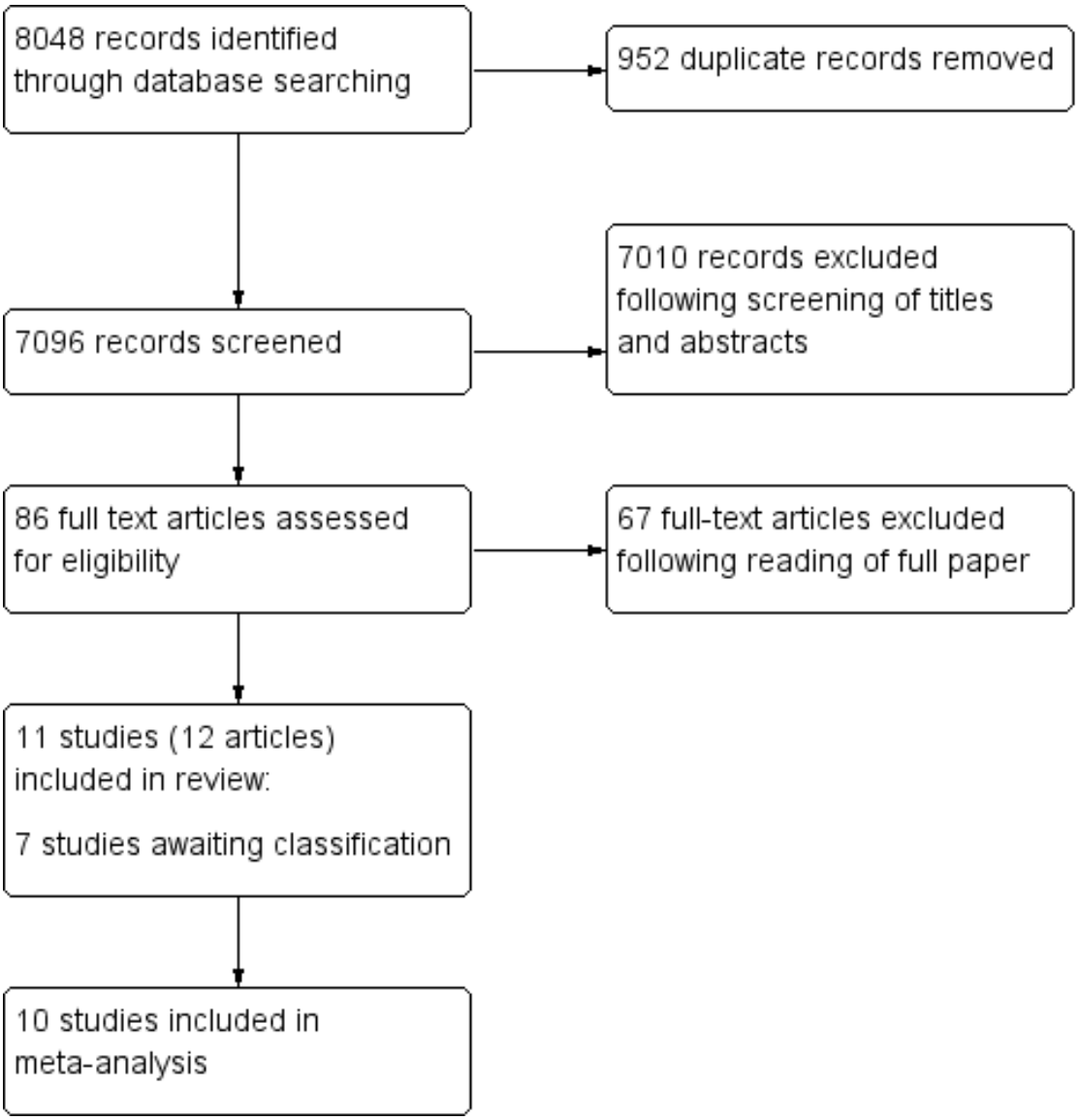
RESULTS

Description of studies

Results of the search

The studies included in this review compare immediate-release methylphenidate versus placebo. See Figure 1 for a flow diagram illustrating the results of the search and the process of screening and selecting studies for inclusion in the review.

Figure 1. Study flow diagram.



We identified 7442 potentially relevant references through searches of the electronic databases conducted in July 2009, June 2011, and October 2012. An updated search on November 27, 2013, and December 12, 2013, identified 606 potentially relevant references.

The searches were conducted by Jo Abbott and Margaret Anderson, Trials Search Co-ordinators of the Cochrane Developmental, Psychosocial, and Learning Problems Review Group, in accordance with our search strategy.

See Appendix 2 for details of the records found at each stage of the search. The grand total of 8048 records can be described as follows.

- 952 were duplicates.
- 5213 records discussed children with ADHD.
- 47 records described pharmacological trials (pharmacokinetics and dynamics).
- 134 records discussed studies in animals.
- 180 records did not discuss methylphenidate.
- 190 records did not discuss ADHD.
- 281 discussed neither methylphenidate nor ADHD.
- 80 were records of genetic studies.
- 21 were records discussing theoretical aspects of ADHD.
- 9 records discussed guidelines for ADHD treatment.
- 60 records discussed neurological or physiological aspects of ADHD and methylphenidate (MPH).

Naturally, many records could be counted in more than one category (eg, a genetics study in children without methylphenidate). These records were allotted to a particular category based on the most defining feature that excluded them from relevance to this review.

The remaining 881 records described studies of adult participants and thus are presented together as follows.

- 70 records were of adult ADHD comorbidities, for example, cocaine dependence or traumatic brain injury.
- 250 were records of nontrials (eg, surveys, case reports).
- 210 were records of reviews of adult ADHD.
- 228 were records of studies in which forms of methylphenidate other than immediate-release were used.
- 61 were records of noncontrolled studies in adults.
- 41 were records in which no clinical ADHD symptoms or general changes were assessed as outcomes.
- 21 were records of potentially relevant reports.

Of the above, 86 full-text articles were assessed for eligibility. Of these, 19 records were judged to be relevant.

Seven were records of conference presentations on the subject of methylphenidate for adults with ADHD. We contacted the speakers to verify whether the data given in these presentations were new and, if so, to obtain said data. We received no replies and so moved these papers to Characteristics of studies awaiting classification. Details of these contacts are provided in Table 2.

This left us with 12 relevant articles, representing 11 studies, which we included in the review. Reference to the relevant article not included appears under Kooij 2004. It is a neurocognitive, outcome-based study pertaining to the same experiment reported by Kooij 2004.

We contacted the first author of each included study. We received kind replies from the following authors: S. Kooij provided us with raw data from the study and further elucidated study methods, as did S. Tenenbaum. Wender replied that all of his work on this subject had been published and provided no further information. The other authors whose studies have been included in this review were contacted but did not reply. For additional details, see Table 2.

Included studies

We included 11 studies in which clinical ADHD symptoms were assessed during or after treatment, or at both times, with immediate-release methylphenidate or placebo.

Duration

All included studies were of relatively short duration: two five-day periods (Gualtieri 1985); two two-week periods (Wood 1976; Wender 1985; Wender 2011); two three-week periods (Kooij 2004); three weeks (Mattes 1984; Spencer 1995); six weeks (Spencer 2005); seven weeks of placebo or active treatment (Kuperman 2001); nine weeks (Bouffard 2003); and 14 weeks (Tenenbaum 2002). It should be noted, however, that Gualtieri 1985, Tenenbaum 2002, and Bouffard 2003 were cross-over studies, and thus active treatment duration was less than half the total trial duration (allowing for washout periods).

Design

Two studies used a parallel-group design (Kuperman 2001; Spencer 2005). The remaining nine studies used a cross-over design.

Sample size

Sample sizes used by studies included in this review were small, with seven studies including 25 to 45 participants. Outliers consisted of studies using very small samples (eight in Gualtieri 1985 and 11 in Wood 1976) and two studies using larger samples of 116 participants (Wender 2011) and 146 participants (Spencer 2005).

Sample sizes (n) were calculated by counting the number of participants from cross-over studies as a single arm and by counting both arms from parallel studies.

Participants

All included studies studied adults, ranging from 17 to 60 years of age and diagnosed with ADHD.

Over the years, some of the diagnostic criteria for the clinical entity now known as ADHD have changed, and one included study dates back to before the time the diagnostic category of ADHD was used. For a discussion of the different diagnostic criteria used by included studies, please see the Quality of the evidence section in the Discussion.

One study (Wood 1976) is dated before publication of the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III)* (APA 1980) (the term "attention deficit" was introduced in *DSM-III*. *DSM-II* included a diagnosis of "hyperkinetic reaction of childhood"). The inclusion criteria used by Wood 1976 can be seen as an equivalent of the *DSM* diagnosis, requiring (1) clinical symptoms of Impulsivity, irritability, restlessness, and emotional lability, (2) a long-standing history of impulsiveness, inattentiveness, short temper, and emotional lability, and (3) a retrospective diagnosis of minimal brain dysfunction in childhood (participants chosen were above the 95th percentile per parent report).

Three studies (Mattes 1984; Gualtieri 1985; Wender 1985) used the criteria from *DSM-III* (APA 1980) to diagnose participants.

One study (Spencer 1995) used criteria from *DSM-III, Revised (DSM-III-R)* (APA 1987) to diagnose participants.

Five studies (Kuperman 2001; Tenenbaum 2002; Bouffard 2003; Kooij 2004; Spencer 2005) used criteria from *DSM-IV* (APA 1994) to diagnose participants.

One study (Wender 2011) used the Utah Criteria for ADHD (Ward 1993) to retrospectively diagnose participants as children, and the Utah Criteria for Adult ADHD (McCann 2000) to ascertain present diagnosis. These criteria are equivalent to those provided in *DSM*, reflecting the core symptom domains of inattentiveness, hyperactivity, and impulsivity.

Interventions

All included studies tested immediate-release methylphenidate versus placebo. A number of studies examined other interventions, as well as methylphenidate and placebo: Tenenbaum 2002 examined Pycnogenol and Kuperman 2001 examined bupropion sustained-release (SR).

Outcomes

Clinical efficacy was defined as improvement in symptoms of ADHD. This primary outcome was evaluated in terms of specific ADHD symptoms-hyperactivity, inattentiveness, and impulsivity-using clinical, symptom-specific scales and scores. These outcomes, whether based on clinical assessment by a physician or by self-report, or with the use of validated or nonvalidated scales, are presented together if they were judged as clinically homogenous.

The outcome of hyperactivity was assessed in the following studies.

- Wood 1976-on an Energetic-Tired scale.
- Wender 1985-by the hyperactivity score on Physician Target Symptom Rating Scale.
- Spencer 1995-by the hyperactivity subscale of ADHD Rating Scale (Barkley 1990).
- Tenenbaum 2002-by the overactivity subscale or the hyperactivity subscale, or both, from Copeland Symptom Checklist (Copeland 1989).
- Kooij 2004-who provided unpublished data for the hyperactivity subscale of *DSM-IV* ADHD Rating Scale (DuPaul 1998).
- Wender 2011-by the hyperactivity score on Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS) (Reimherr 2003).

The outcome of impulsivity was assessed in the following studies.

- Wood 1976-on a cool-tempered/hot-tempered scale.
- Spencer 1995-by the impulsivity subscale of ADHD Rating Scale (Barkley 1990).
- Tenenbaum 2002-by Barratt Impulsiveness Scale (Barratt 1985).
- Kooij 2004-who provided unpublished data for the inattention subscale of *DSM-IV* ADHD Rating Scale (DuPaul 1998).
- Wender 2011-by the impulsivity score on WRAADDS (Reimherr 2003).

The outcome of inattentiveness was assessed in the following studies.

- Wood 1976-on a concentrating-mind wandering scale.
- Wender 1985-by the "short attention span" score on Physician Target Symptom Rating.
- Spencer 1995-by the inattentiveness subscale of ADHD Rating Scale (Barkley 1990).
- Tenenbaum 2002-by Brown Attention Deficit Disorder Scales (Brown 1996).
- Kooij 2004-who provided unpublished data for the inattention subscale of *DSM-IV* ADHD Rating Scale (DuPaul 1998).
- Spencer 2005-by inattentive ADHD symptom scores. Data for this outcome were estimated from a graph presentation.
- Wender 2011-by the attention difficulties score on WRAADDS (Reimherr 2003).

The only outcome reporting clinical change in symptoms of ADHD used by Gualtieri 1985 was the Adult Activity Scale (AAS). This 14-item rating scale is based on Conners Parent/Teacher

Questionnaire. We were not able to obtain the AAS nor to ascertain the ADHD domains covered by this scale nor how this scale was adjusted for adults. Therefore, we do not know whether this scale reports on specific domains of ADHD or on general change in ADHD severity; consequently we were not able to include this scale in any meta-analysis.

Secondary outcome measures were evaluated by assessing overall change in condition, as expressed by CGI (Clinical Global Impression Scale) and other scales as outcomes of continuous data, and overall change in condition as an outcome of dichotomous data.

The outcome of overall change through continuous data was assessed by the following studies.

- Mattes 1984-by a global improvement rating.
- Wender 1985-on Physician Global Rating Scale, similar to CGI Scale.
- Kuperman 2001-who reported changes on self-rated ADHDRS (ADHD Symptom Checklist Severity) (Barkley 1990).
- Tenenbaum 2002-assessed overall change using several different scales (Barkley's ADHD Rating Scale, Copeland Symptom Checklist for Adult Attention Deficit Disorders, and Attention Deficit Scale for Adults Scale). We chose to incorporate data from Copeland Scale (Copeland 1989) because this scale contains subscales for the three domains of inattentiveness, hyperactivity, and impulsivity.
- Bouffard 2003-by changes on Conners Rating Scale (Conners 1994). Data for both a higher dose (15 mg three times daily) and a lower dose (10 mg three times daily) were provided. We opted to include data for the higher dose used.
- Kooij 2004-by changes on CGI scale.
- Spencer 2005-by changes on CGI scale.
- Wender 2011-by changes on the total score of WRAADDS (Reimherr 2003).

The outcome of overall change through dichotomous data was assessed using data from the following studies.

- Wender 1985-who defined responders as those with a moderate to marked treatment response on Physician Global Rating Scale.
- Spencer 1995-who defined responders as participants who had a CGI score of two or less or a 30% reduction in individual rating scale scores.
- Kuperman 2001-who reported on responders versus nonresponders (responders were those who improved on one or more CGI scores, as rated by a clinician).
- Spencer 2005-who defined responders as those who had a "much" or "very much" improved CGI score and a 30% reduction in AISRS (Adult ADHD Investigator System Report Scale) score (Spencer 2004).
- Wender 2011-who defined responders as those experiencing at least a 50% reduction in total WRAADDS score.

In addition to these outcomes, Kuperman 2001, Tenenbaum 2002, Bouffard 2003, and Boonstra 2005 (a part of Kooij 2004), assessed participants using Conners Continuous Performance Test (CPT). We chose not to include CPT results in the review, as the focus of this review was clinical rather than neuropsychological.

Reports of changes in general mental state were assessed as follows: Almost all of the 11 studies using clinical outcomes included some assessment of anxiety and depression. Most did so using Hamilton Scales for Depression and Anxiety (Spencer 1995; Kuperman 2001; Bouffard 2003; Kooij 2004; Spencer 2005) or Beck Depression Inventory (Tenenbaum 2002; Bouffard 2003; Spencer 2005). Unfortunately, very few supplied results for baseline versus end of trial for immediate-release methylphenidate and placebo (anxiety: Gualtieri 1985 on Zung Self-Rating Anxiety Scale; Kuperman 2001 and Bouffard 2003 on Hamilton Anxiety Scale; and Tenenbaum 2002 on Beck Anxiety Inventory; depression: Gualtieri 1985 on Zung Self-Rating Depression Scale; Kuperman 2001 on Hamilton Depression Scale; Tenenbaum 2002 and Bouffard 2003 on Beck Depression Inventory).

Adverse effects were specifically reported or measured in eight studies (Mattes 1984; Wender 1985; Spencer 1995; Kuperman 2001; Bouffard 2003; Kooij 2004; Spencer 2005; Wender 2011). Gualtieri 1985 measured pulse and blood pressure for all participants but did not specifically report these results under adverse effects, and did not present other reports of adverse effects. Two studies (Wood 1976; Tenenbaum 2002) did not mention adverse effects.

Location

All but two of the included studies were conducted in the USA: two in the Boston area (Spencer 1995; Spencer 2005), three in the Salt Lake City area (Wood 1976; Wender 1985; Wender 2011), and one in North Carolina (Gualtieri 1985). Mattes 1984, Kuperman 2001, and Tenenbaum 2002 also conducted their studies in the USA, but it is not clear where. Of the remaining two studies, one was conducted in Canada (Bouffard 2003) and the other in the Netherlands (Kooij 2004).

Risk of bias in included studies

Allocation

One trial (Kooij 2004) reported adequate sequence generation. The other 10 studies were judged to have unclear risk of bias regarding sequence generation. All studies were judged to have unclear risk of bias with regard to allocation concealment; it was not clear how randomization to treatment groups had occurred or what measures, if any, had been taken to secure adequate allocation concealment.

Two of the included trials used a parallel-group design (Kuperman 2001; Spencer 2005). The remainder were cross-over trials in

which each participant served as his or her own control (allocation to start of treatment vs placebo arm was random).

Blinding

All trials were reported to be double-blind. Five studies (Wood 1976; Mattes 1984; Kuperman 2001; Bouffard 2003; Wender 2011) reported no procedure to guarantee double-blinding and therefore received a judgement of unclear risk of bias with regard to blinding. In Kuperman 2001, treatment and placebo were given at the same time, but no specifics were given as to the appearance of the placebo pills. Bouffard 2003 did not specify identical appearance or whether treatment and placebo were dispensed at the same time, and Wood 1976, Mattes 1984, and Wender 2011 reported no method guaranteeing participant or investigator blinding. Gualtieri 1985 was judged as having high risk of bias as no information was given about measures taken for blinding and all participants were able to accurately guess the active drug condition.

In five trials (Wender 1985; Spencer 1995; Tenenbaum 2002; Kooij 2004; Spencer 2005), details were provided as to procedures used to ensure blinding; thus these studies were judged to be at low risk of bias.

Incomplete outcome data

Of the trials included, three reported no dropouts (Wood 1976; Gualtieri 1985; Kooij 2004) and thus were judged to have low risk of bias for incomplete outcome data. Spencer 2005 was also judged to have low risk of bias for incomplete outcome data, as dropout was balanced across groups, and of the reasons given for dropout, only "no effect" was statistically significant.

Mattes 1984, Tenenbaum 2002, Bouffard 2003, and Wender 2011 reported dropouts but did not report from which groups or whether dropout was balanced across groups, and in some cases, reasons for discontinuation were not provided. No intention-to-treat (ITT) analysis was carried out, and these studies were judged to have unclear risk of bias with regard to incomplete data. Wender 1985 was also thus judged, as no information was provided about dropouts.

Kuperman 2001 alone, with a dropout rate of six out of 37 (16%), analyzed all participants completing the first week of randomized treatment. However, although a last observation carried forward (LOCF) approach was used, this was applied after seven participants (of the original 37 randomly assigned) had dropped out, and exact numbers of dropouts per treatment group and reasons were not given. Therefore, this study was judged to have unclear risk of bias with regard to incomplete data.

See Table 3 for additional information.

Selective reporting

In general, for most studies, prestated outcomes were reported and studies were judged as having low risk of bias. Mattes 1984 did not report all of the study's prespecified primary outcomes, and Spencer 2005 reported some outcomes incompletely. These two studies were judged to have high risk of bias.

Other potential sources of bias

For four studies (Wood 1976; Wender 1985; Tenenbaum 2002; Wender 2011), information was insufficient to allow assessment of whether an important risk of bias existed; therefore these studies were judged to be at unclear risk for other potential sources of bias. Gualtieri 1985 was judged as having high risk of bias from other potential sources; it was not clear on what basis specific participants were selected to take part in the efficacy study. In addition, participants took part in a number of experimental protocols over a three-year period, and it is not clear how much time elapsed between initial characterization and recruitment until the efficacy study commenced.

The remaining six studies were judged to be at low risk for other sources of bias.

Three of the cross-over studies (Wood 1976; Mattes 1984; Wender 2011) did not include a washout period between different periods of intervention. The fact that no washout period was included may be assumed to be a source of additional bias. However, immediate-release methylphenidate has a pharmacokinetic half-life of two to three hours (Kimko 1999), weakening the importance of having a washout period. In addition, methylphenidate has been found to be susceptible to detection by participants in double-blind studies. Therefore, we do not think that lack of a washout period constitutes a significant additional source of bias in these studies.

Publication bias

To investigate a relationship between effect size and study precision (closely related to sample size), a funnel plot is usually used. However, in this review the number of studies for all outcomes was too small to allow testing for publication bias; therefore funnel plots were not used (see also Egger 1997).

See Figure 2 for a "Risk of bias" graph showing the review authors' judgements about each item presented as percentages across all included studies. See Figure 3 for a graphic summary of the review authors' judgements about each risk of bias item for each included study.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

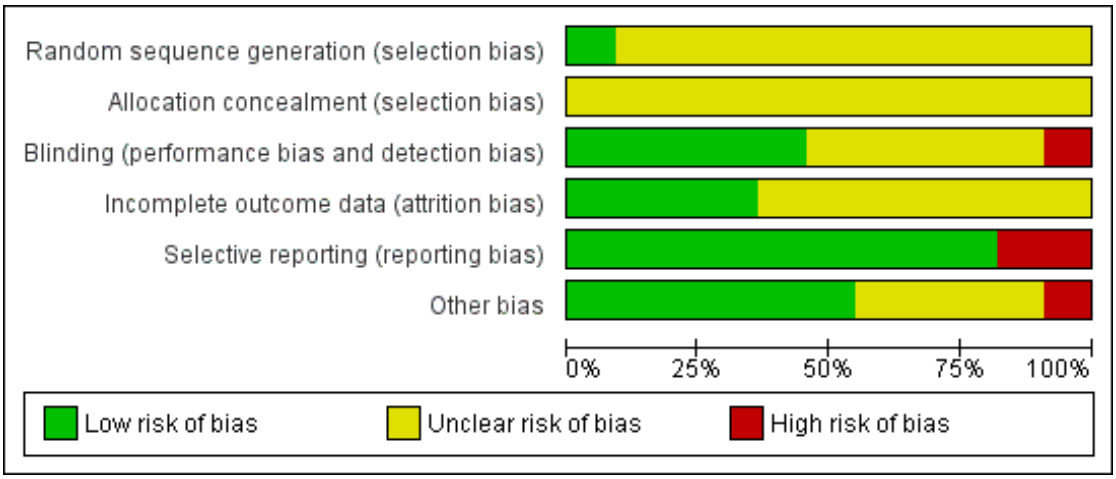
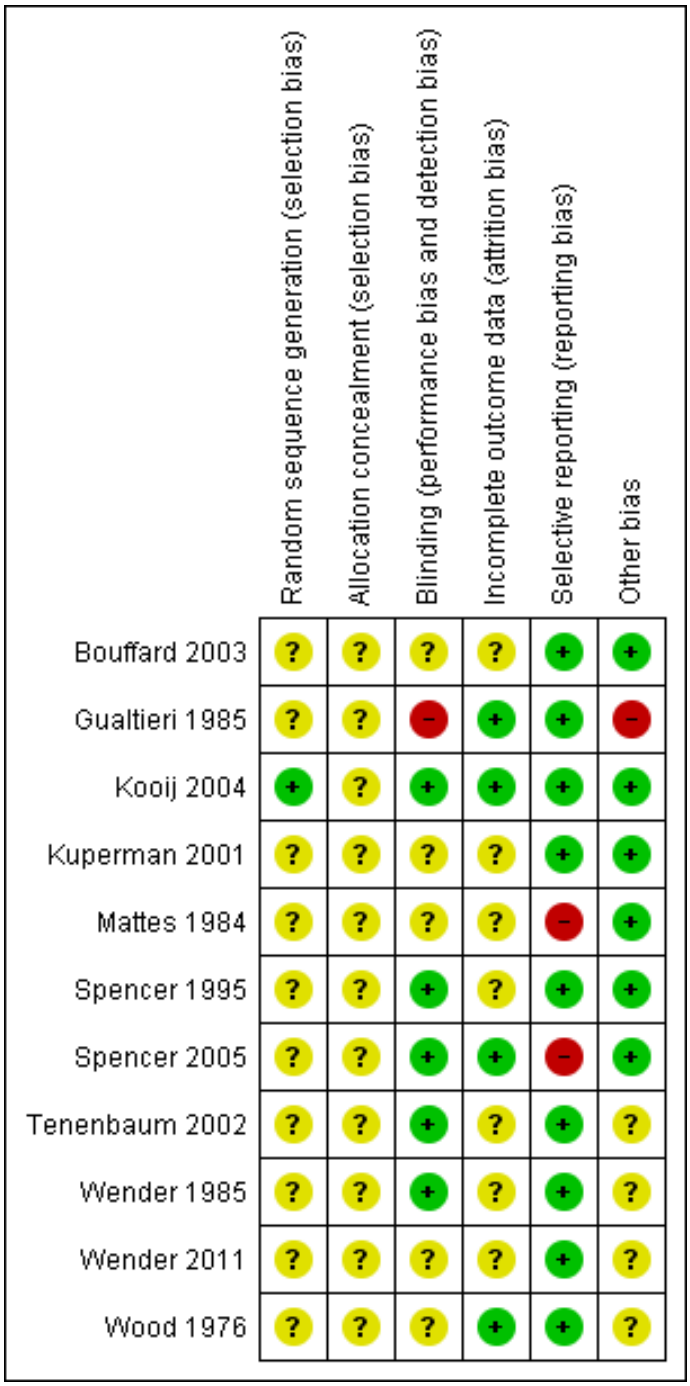


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



We have provided additional information about the methodological quality of trials in the Characteristics of included studies tables.

Effects of interventions

See: **Summary of findings for the main comparison** Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults

It was our intention to perform a pooled analysis of the different results obtained. At first, it appeared that heterogeneity was too great for synthesis to take place. However, a decision not to synthesize the data would have led to a description such as "vote counting," which is also misleading. Therefore, we opted to synthesize the data using a random-effects model to incorporate heterogeneity. We discuss the limitations this poses when explaining the results in the Discussion section.

Primary outcomes

For the purpose of this review, clinical efficacy was defined by the review authors as improvement in the main symptoms of ADHD (hyperactivity, impulsivity, and inattentiveness) and in overall change. The included studies used different scales developed for use in children with ADHD and adjusted for adults, or scales developed specifically for adults. We have taken this into account when dealing with the data, by addressing the main diagnostic features of adult ADHD and those shared by all or most studies-inattentiveness, impulsivity, and hyperactivity-as the outcomes of greatest significance in evaluating symptom severity and treatment efficacy.

Hyperactivity

The outcome of hyperactivity was assessed by six studies (Wood 1976; Wender 1985; Spencer 1995; Tenenbaum 2002; Kooij 2004; Wender 2011) using several different scales. These studies used a cross-over design. As different scales were used in various studies for this outcome measure, we used the SMD to compare results. For this outcome, we treated Wood 1976 and Wender 1985 as having parallel design, as they had negative correlation coefficients.

We synthesized the data using a random-effects model, with an average intervention effect of -0.60 (95% confidence interval (CI) -1.11 to -0.09; N = 245) (Analysis 1.1). We observed a large amount of statistical heterogeneity (I^2 = 88%). See Table 4 for individual study results.

Impulsivity

The outcome of impulsivity was assessed by five studies (Wood 1976; Spencer 1995; Tenenbaum 2002; Kooij 2004; Wender 2011) using different scales. These studies used a cross-over design. As different measures were used in various studies for this outcome measure, we used the SMD to compare results.

Spencer 2005 presented combined data regarding change in the domains of hyperactivity and impulsivity. For this reason, we were not able to include those data in our analysis. Spencer 2005 found a decrease in symptoms of impulsivity/hyperactivity of 15 (± 1) to 11 (± 1) for the placebo group (week zero vs week six) as opposed to a decrease of 13.8 (± 0.5) to 5 (± 0.5) for the methylphenidate group (week zero vs week six).

We synthesized the data using a random-effects model, with an average intervention effect of -0.62 (95% CI -1.08 to -0.17; N = 207, I^2 = 81%) (Analysis 1.2). See Table 5 for each study's results.

Inattentiveness

Data for the outcome of inattentiveness were synthesized from seven studies: one parallel-group study (Spencer 2005) and six cross-over studies (Wood 1976; Wender 1985; Spencer 1995; Tenenbaum 2002; Kooij 2004; Wender 2011). Although It is generally advisable to conduct separate meta-analyses for parallel-group and cross-over trials, irrespective of whether they are also combined, in the case of the outcome of inattentiveness we chose not to do so because of the fact that only one parallel study was included. As different scales were used in these studies, we found it appropriate to use the SMD as the metric of choice (Curtin 2002b). Given that Wender 1985 had a negative correlation coefficient, we treated this study as parallel.

We synthesized the data using a random-effects model, with an average intervention effect of -0.66 (95% CI -1.02 to -0.30, N = 391, I^2 = 76%) (Analysis 1.3). See Table 6 for each study's results.

Subgroup analysis-dosage

To see whether dosage affected the results, we conducted a subgroup analysis. Studies were divided into those in which participants were given more than 0.9 mg/kg/d and those in which participants were given less than 0.9 mg/kg/d. The dosage of 0.9 mg/kg/d was chosen to divide low dose from high dose because (1) doses in the range of 60 to 70 mg per day and above are considered clinically to be high doses (making the dose for a 75-kg adult in the area of 0.9 mg/kg); and (2) studies that reported dispensing higher doses used doses of 1 mg/kg/d or higher, making 0.9 mg/kg/d a reasonable dividing point. The purpose of this analysis was twofold. First, we wanted to examine whether a higher dose of immediate-release methylphenidate would be associated with improved efficacy, in accordance with our prespecified Subgroup analysis and investigation of heterogeneity section. Second, we wished to examine the possibility that the high level of heterogeneity encountered was due to different dosages used in the pooled

studies (with higher doses producing a significantly different effect). This was done with the understanding that exploring heterogeneity when a small number of studies is involved is of questionable value (Higgins 2003).

Low dose

Studies pooled in this category reported a dose of less then 0.9 mg/kg/d (Wood 1976; Wender 1985; Tenenbaum 2002; Wender 2011). The direction of the effect for each of the three outcomes analyzed favored treatment (Analysis 1.4). The size of the effect ranged from -0.61 for the outcome of hyperactivity (I^2 = 90%), to -0.62 for the outcome of impulsivity (I^2 = 75%), to -0.84 for the outcome of inattentiveness (I^2 = 73%), in favor of immediate-release methylphenidate. Individual results for this subgroup analysis are presented in Table 7; see Table 8 for original data.

High dose

Studies pooled in this category were Spencer 1995, Kooij 2004, and Spencer 2005. The direction of the effect in this subgroup analysis, which included only two studies for two outcomes and all three for the outcome of inattentiveness, favored treatment with immediate-release methylphenidate. The direction of the effect for each of the three outcomes analyzed also favored treatment (Analysis 1.5). The size of the effect ranged from -0.44 for the outcome of inattentiveness (I^2 = 58%), to -0.63 for the outcome of hyperactivity (I^2 = 90%), to -0.76 for the outcome of impulsivity (I^2 = 87%), in favor of immediate-release methylphenidate. The number of individuals displayed in the plot and analysis is the number per arm, hence counting participants in the cross-over trials twice (in this case, Spencer 1995, Kooij 2004, and Spencer 2005, all of parallel design).

Individual results for this subgroup analysis are presented in Table 9.

As the 95% CIs of high dose and low dose overlap, the data show no differences between doses. Evidence from the subgroup analysis does not indicate that a higher dose of immediate-release methylphenidate is associated with higher efficacy-an observation that is limited by the few and generally small studies included.

Secondary outcomes

Overall change

Overall change in condition was reported by eight studies using continuous data and by five studies using binary data. Binary data were transformed to SMD and respective SE (Higgins 2008; Section 9.4.6). To facilitate synthesis of both binary and continuous outcomes, when a study presented both continuous and dichotomous data for overall change in condition (Wender 1985; Kuperman 2001; Spencer 2005; Wender 2011), we transformed all outcomes to SMD and SE and then decided which to include in the meta-analysis based on our predefined criteria. In the presentation of data, we retained "binary" and "continuous" subgroups to represent types of outcomes. However, none of these included all available data, if treated separately. Joint analysis of included studies with continuous (Table 10) or binary (Table 11) data for the outcome of overall change showed an SMD of -0.72 (95% CI -1.12 to -0.32) in favor of immediate-release methylphenidate (N = 455) with evidence of large statistical heterogeneity (I^2 = 77%).

The only outcome reporting clinical change in symptoms of ADHD used by Gualtieri 1985 was the Adult Activity Scale (AAS). This 14-item rating scale is based on Conners Parent/Teacher Questionnaire. We were not able to obtain AAS nor to ascertain the ADHD domains covered by this scale nor how this scale was adjusted for adults. Therefore, we do not know whether this scale reports on specific domains of ADHD or on general change in ADHD severity; consequently we were not able to include this scale in any pooled analysis; it is not clear what this outcome actually reports. In any case, no important differences were found between methylphenidate and placebo for this outcome.

General mental state changes

Anxiety and depression

Results for anxiety and depression as parameters of general changes in mental state are equivocal, with some trials reporting a reduction in anxiety and depression using immediate-release methylphenidate, others noting no change, and still others describing an increase in anxious and depressive symptoms.

One study (Wender 2011) did not evaluate anxiety or depression. Because of the different scales and reporting methods used, we chose not to conduct a meta-analysis of results for the effects of immediate-release methylphenidate on measures of anxiety or depression.

Some studies evaluated anxiety or depression but did not report numerical findings, or reported partial findings that could not be combined: Mattes 1984 used Profile of Mood States scale with no numerical reports; Spencer 1995 assessed anxiety and depression using Hamilton Anxiety Scale, Hamilton Depression Scale, and Beck Depression Inventory but did not report numerical results; Kooij 2004 assessed anxiety and depression using Hamilton Anxiety Scale and Hamilton Depression Scale but reported data that could not be combined; Spencer 2005 assessed anxiety and depression using Hamilton Anxiety Scale, Hamilton Depression Scale, and Beck Depression Inventory but did not report numerical results.

Other studies reported findings but evaluated anxiety or depression using heterogenous scales and measures: Wender 1985 used Profile of Mood States and Beck Depression Inventory (reporting endpoint means); Bouffard 2003 evaluated anxiety and depression using Beck Depression Inventory and Hamilton Anxiety

Scale (reporting baseline and endpoint data); Wood 1976 evaluated anxiety and depression using a "calm-nervous" and "happy-sad" scale; Kuperman 2001 evaluated anxiety and depression using Hamilton Anxiety Scale and Hamilton Depression Scale, and reported baseline and change data; Tenenbaum 2002 evaluated anxiety and depression using Beck Anxiety Inventory and Beck Depression Inventory, reporting on baseline and endpoint data; Gualtieri 1985 evaluated anxiety and depression using Zung Self-Rating Anxiety Scale and Zung Self-Rating Depression Scale, and reported on baseline and endpoint data.

Bouffard 2003 noted a significantly greater reduction in anxiety and a trend toward greater reduction in depression with immediate-release methylphenidate over placebo. Gualtieri 1985, Kuperman 2001, and Spencer 2005 found no important differences on measures of anxiety and depression between placebo and immediate-release methylphenidate, but evidence of "mild moodiness" was reported by Spencer 2005.

Kooij 2004 described higher anxiety and depression scores for the immediate-release methylphenidate group, and Tenenbaum 2002 found immediate-release methylphenidate to be significantly less effective than placebo in reducing anxiety and depression. Spencer 1995 reported that only two participants had severe symptoms of anxiety at baseline, as measured on Hamilton Anxiety Scale; therefore it was not possible to evaluate the impact of treatment on this rating scale score. Spencer 1995 reported that anxiety increased by 22% (5/23) in the immediate-release methylphenidate group and did not report anxiety in the placebo arm.

Because of different scales and reporting methods used, and because most studies reported no numerical results or reported results that could not be combined, we chose not to conduct a meta-analysis of results for the effects of immediate-release methylphenidate on measures of anxiety or depression. A meta-analysis of these results would be partial and misleading.

Global assessment of functioning (GAF)

Four
trials examined the effects of immediate-release methylphenidate on overall functioning using GAF (Bouffard 2003; Kooij 2004; Spencer 2005; Wender 2011) but did not supply complete data for this scale. Kooij 2004 described a nonsignificant 2.5-point increase in GAF score for the immediate-release methylphenidate group, and Spencer 2005 described an across-the-board improvement for both experimental and control groups, with immediate-release methylphenidate showing more robust improvement than placebo, which increased with the duration of the trial. Bouffard 2003 found a significant six-point difference in the immediate-release methylphenidate group between baseline and end of study in favor of treatment-an increase that was not found for placebo.

Adverse effects

Appetite and weight loss

The most pronounced adverse effect noted was loss of appetite. Rates of reported appetite loss during treatment with immediate-release methylphenidate were reported by six studies (Mattes 1984; Spencer 1995; Kuperman 2001; Bouffard 2003; Kooij 2004; Spencer 2005) and varied from 41% in the Bouffard 2003 study, to 27% in the large Spencer 2005 study, to 7% in Wender 2011. Weight loss, therefore, would be a matter of concern, given the rates of reported appetite loss. Indeed, weight loss in the immediate-release methylphenidate group was reported in three trials: Kooij 2004 reported that mean weight was 1.7 kg lower in the immediate-release methylphenidate group compared with the placebo group after the three-week trial; Spencer 1995 reported a mean loss of 1.2 kg after a three-week trial; and Spencer 2005 reported an average weight loss of 2.4 kg in the immediate-release methylphenidate group after a six-week trial. In Wender 1985, one participant reported loss of appetite and a 4.5-kg weight loss on methylphenidate.

Heart rate and blood pressure

An increase in systolic blood pressure in the immediate-release methylphenidate group was reported by Bouffard 2003, and a significant increase in heart rate was reported by Spencer 1995 and Spencer 2005. Kooij 2004 reported a non-statistically significant rise in heart rate and in systolic blood pressure, and Spencer 1995 noted a non-statistically significant rise in both systolic and diastolic blood pressures. Gualtieri 1985 reported a small and non-significant rise in pulse and in systolic and diastolic blood pressures. No study reported any clinically significant cardiovascular adverse effects.

Other adverse effects

Another reported adverse effect was insomnia, as reported by Wender 1985, Spencer 1995, Kuperman 2001, and Wender 2011 (although this was not significant). Aside from insomnia, Kuperman 2001 reported tremor, sweating, and jitteriness in two out of 12 participants from the immediate-release methylphenidate group, which were not reported at all in the placebo group. In this study, however, a similar number of adverse effects were reported among the three treatment groups: immediate-release methylphenidate, placebo, and bupropion sustained-release (SR). In Wender 2011, the most common adverse effect was headache; this was reported significantly more often in the treatment group in Mattes 1984 as well. Mattes 1984 further reported that late-afternoon depression appeared significantly more often in the treatment group. "Mild moodiness" was reported by Spencer 2005, who also reported the adverse effect of dry mouth. In addition to insomnia, Wender 1985 reported the adverse effects of mild anxiety, jaw tension, tooth grinding, overstimulation, irritability, and nose tingling. This study does not mention to what

extent these adverse effects were prevalent or significant. Wender 1985 further reported on one participant who had what was defined as a serious side effect of anger with poor concentration while receiving placebo.

No reporting of adverse effects

Two studies (Wood 1976; Tenenbaum 2002) did not mention adverse effects. We were unable to determine whether this was done because no adverse effects occurred or because no data were collected.

See Table 12 for specific data.

Adverse effects were not systematically reported. In some cases, it was not clear whether adverse effects occurred. In most cases when adverse effects were reported, no numerical results were given. Therefore, we were unable to conduct a meta-analysis of the outcomes of adverse effects.

Death

No study reported deaths among participants.

Original data for all of these analyses can be found in Table 8.

DISCUSSION

Summary of main results

Our search yielded 11 relevant studies. Clinical response to immediate-release methylphenidate was evaluated by both change in specifically defined ADHD symptoms and overall change.

For each outcome, when no identical scales were available in different studies, we synthesized clinically homogenous scales, be they physician or nonphysician rated, validated or nonvalidated.

Outcome measurements of specific ADHD symptoms, such as hyperactivity, impulsivity, and inattentiveness, demonstrated improvement under treatment with immediate-release methylphenidate. In studies reporting the impact of immediate-release methylphenidate on hyperactivity, effect sizes between -0.21 and -1.38 were observed in favor of treatment, with one study reporting an effect size of 0.39 in favor of placebo. For this outcome, the average intervention effect was -0.60 in favor of immediate-release methylphenidate.

Effect sizes for impulsivity ranged from -0.23 to -1.42 in favor of immediate-release methylphenidate and were found across four of the five included studies, with one study reporting an effect size of 0.05 in favor of placebo. The average intervention effect was -0.62 in favor of immediate-release methylphenidate.

For the outcome of inattentiveness, all seven studies reported effect sizes in the range of -0.02 to -1.46 in favor of immediate-release methylphenidate. The average intervention effect was -0.66 in favor of immediate-release methylphenidate.

Tenenbaum 2002 consistently reported an advantage for placebo over immediate-release methylphenidate.

A subgroup analysis of high versus low doses of immediate-release methylphenidate was conducted. Results do not indicate that a higher dose of immediate-release methylphenidate was associated with higher efficacy, and they do not lend support to the current recommendation of immediate-release methylphenidate doses of up to 1.3 mg/kg/d (Biederman 2006a)-an observation that is limited by the few and generally small studies included.

In all outcomes, we observed evidence of large statistical heterogeneity (I^2 > 75%) that could not be explained by differences in dosage. The number of studies per outcome was not adequate to permit proper exploration of possible sources of heterogeneity. This heterogeneity could have several causes, one of which could be varying participant characteristics pertaining to, for example, ADHD subtype and severity. It may also be hypothesized that adult ADHD presentation has changed over the 35 years spanned by the included studies. Over those years, rates of undiagnosed children, especially in the USA, have declined, and diagnosed and treated children may present differently than untreated ones as adults.

For overall change, the SMD was -0.72 in favor of immediate-release methylphenidate (95% CI -1.12 to -0.32, n = 455).

Adverse effects

The most pronounced adverse reaction noted was a decrease in appetite, with reported values ranging from 41% on immediate-release methylphenidate versus 19% on placebo (Bouffard 2003), to 22% immediate-release methylphenidate versus 4% on placebo (Kooij 2004), to 27% on immediate-release methylphenidate versus 7% on placebo (Spencer 2005). Three studies reported significant concomitant weight loss in the immediate-release methylphenidate group. Weight lost ranged from 1.1 kg (Spencer 1995) to 1.7 kg on average (Kooij 2004) in these three-week trials, and the largest weight reduction averaged 2.4 kg in a six-week study (Spencer 2005). The clinical significance of the weight loss is difficult to determine because of the short duration of the studies, with the longest trial included in this review lasting six weeks.

Spencer 2005 reported an adverse effect of mild moodiness (30% on immediate-release methylphenidate vs 10.7% on placebo). One study (Kuperman 2001) reported similar rates of adverse effects with immediate-release methylphenidate and placebo, and Spencer 1995 reported similar rates of subjective adverse effects with immediate-release methylphenidate and placebo but indicated that these adverse effects were more pronounced with the active medication. Two studies (Wood 1976; Tenenbaum 2002) did not report adverse effects. It should be noted that none of the adverse effects were of a serious nature.

Overall completeness and applicability of evidence

Studies included in this review allow us to address our objective-to determine the efficacy and tolerability of immediate-release methylphenidate in the treatment of adults with ADHD. However, these results may be applicable only to studies of a similarly short duration. As is the case with other *DSM-IV-TR* disorders, and because of the nature of psychiatric disorders, many types of relevant participants and outcomes were not investigated by the review authors and were not investigated by the authors of the included studies. For example, ADHD may be diagnosed in the presence of different comorbidities that may influence outcomes. A specific type of outcome that would have been valuable is an outcome measure of overall functioning or quality of life, especially after a long course of treatment. Only three studies provided data on GAF scores that we were unable to synthesize and that were based on studies of short duration. It was our intention to investigate only immediate-release methylphenidate. Future reviews can assess different interventions for adults with ADHD, although the number of relevant studies, we fear, is sparse.

The objective of most of the studies included in this review was the same as the objective of the review itself, making their evidence highly relevant. We believe that the external validity of this review is fair, and that one may generalize the causal inference from the sample studied to the defined target population. Because of the highly cultural aspects of psychiatric disorders, ADHD among them, we advise caution in generalizing results of this review to non-Western culture populations, especially because this review did not include studies from such populations.

Quality of the evidence

This review includes studies spanning 35 years (Wood 1976 to Wender 2011). As is the case for many other psychiatric diagnoses, diagnostic methods, practices, and criteria for ADHD are evolving, change periodically, are adapted and used selectively, and are the topics of discussion and research. That being said, the core diagnostic criteria have been stable and consistent over the years, based on the core symptoms of hyperactivity, impulsivity, and inattentiveness. Differences between diagnostic classifications are minor and include varying degrees of hyperactivity and inattentiveness. As *DSM-IV* criteria are broad and inclusive, all participants who met diagnostic criteria according to earlier diagnostic classifications would have received a *DSM-IV* diagnosis today. For this reason, we believe that these earlier studies should be included in this review.

Only a small number of placebo-controlled randomized studies examining use of immediate-release methylphenidate for adult ADHD were found. This finding is surprising, given the high prevalence of the disorder and its far-reaching implications and consequences, including low academic performance, impaired driving skills, decreased employment, and marital instability.

Studies found were generally of short duration, ranging from five days to six weeks for studies using clinical outcomes. Most studies included only a small number of participants (exceptions include Spencer 2005, which included more than 140 participants, and Wender 2011, with 105 participants).

All but two studies (Kuperman 2001; Spencer 2005) used a crossover design, and all but one (Kooij 2004) failed to provide data on the individual endpoints of each trial arm. Different studies included in this review used different scales for different outcome measures and different scales for similar outcome measures.

All studies were judged to have unclear risk of allocation concealment bias (selection bias). Five studies were judged to have low risk of blinding bias (Wender 1985; Spencer 1995; Tenenbaum 2002; Kooij 2004; Spencer 2005). Ten studies were judged to have low risk of selective reporting bias.

For all outcomes except inattentiveness, the quality of evidence was assessed as "high" according to the GRADE approach. For the outcome of inattentiveness, most information was derived from studies judged to have unclear risk of bias; therefore the quality of evidence for this outcome was judged as "moderate" in keeping with the GRADE approach.

Because the quality of evidence was assessed as moderate for the outcome of inattentiveness, we considered whether we should downgrade the primary outcome measure for inconsistency. We chose not do so for a number of reasons: (1) The GRADE rating for the outcome of inattentiveness was downgraded because most information was derived from studies judged to have unclear, but not high, risk of bias. In this case, the GRADE guidelines, in the matter of going from assessments of risk of bias to judgements about study limitations for main outcomes, recommend not downgrading the GRADE assessment of the main outcome (Higgins 2011; Table 12.2.d); (2) taken as a whole, the body of evidence includes some factors that may increase the quality level, such as a large magnitude of effect. Factors that may decrease the quality level of a body of evidence are associated mainly with heterogeneity or inconsistency of results of subgroup analyses (Higgins 2011). Results of this analysis may indicate not that a higher dose of immediate-release methylphenidate is associated with higher efficacy, but rather that the data show no differences between doses, and that the meaning of the results of the subgroup analysis are limited by the few and generally small studies included. We therefore chose not to attribute excessive weight to inconsistency from this subgroup analysis.

Summary of findings for the main comparison includes GRADE ratings for specific outcomes.

Potential biases in the review process

The search process was performed in such a way that it minimized bias in the compilation of potentially relevant references. This was a result of the fact that the search was conducted according to

search criteria recommended by staff at The Cochrane Collaboration.

We repeatedly attempted to contact authors of all included studies but often received no reply. Replies to our inquiries may have supplied us with additional data and allowed for a more comprehensive evaluation of different biases in each of our included studies, and for more studies to be represented for each of the different outcome measures. We can only speculate as to reasons why cooperation was limited.

We classified seven reports as "Studies awaiting classification" (see Characteristics of studies awaiting classification). These were all reports of conference presentations. We contacted the relevant speakers to inquire whether any of these presentations included unpublished data. Wender replied that these reports did not refer to unpublished studies. We were unable to obtain replies from the other authors and therefore considered these reports as awaiting classification.

Agreements and disagreements with other studies or reviews

Several meta-analyses of randomized, placebo-controlled studies comparing pharmacological interventions for ADHD have been published. Meszaros 2009 conducted a meta-analysis of the therapeutic efficacy of various pharmacological treatments for adults with ADHD based on data from controlled clinical trials. He reported that the pooled effect size across all treatments was in the medium to high range (Cohen's d = 0.65, P value < 0.0001 vs placebo), and that the effect size for stimulants (Cohen's d = 0.67, P value < 0.0001 vs placebo) was somewhat higher than for non-stimulant medications (Cohen's d = 0.59, P value < 0.0001 vs placebo). This corresponds to the findings of Faraone 2004, who analyzed the literature on different pharmacological interventions for ADHD to describe the variability of drug/placebo effect sizes. He included studies among youth and reported that effect sizes for stimulants were significantly greater than those for other medications.

Peterson 2008 assessed comparative benefits and harms of competing medications for adult ADHD and included 22 placebo-controlled trials. He reported that the relative benefit of the clinical response for shorter-acting stimulants (primarily immediate-release methylphenidate) was 3.26 times greater than for longer-acting stimulants (95% CI 2.03 to 5.22) and 2.24 times greater than for longer-acting forms of bupropion (95% CI 1.20 to 4.08). Peterson described medication effectiveness as "evidence of academic, occupational, social, and/or legal outcomes, and of complete symptom remission. Efficacy outcomes were incidence of clinical response and change from baseline in ADHD symptom scores ... clinical response was most commonly defined as the proportion of patients with a 30% or greater improvement in ADHD-RS Total Score" (p 3). The first part of Peterson's outcome measure does not correspond to the outcome measure used in this review. The second part of Peterson's outcome measure may be compared with what we have defined as overall change. Quantitatively, it is not possible to compare our findings with those of Peterson. Qualitatively, Peterson's findings support our findings of efficacy of immediate-release methylphenidate for adults with ADHD. Peterson limited his comparisons of adverse events to sleep or appetite disturbances, anxiety, and serious cardiovascular event outcomes. He concluded that "adverse event reporting was sparse in placebo-controlled trials" and that "overall, shorter-acting stimulants, longer-acting stimulants, and atomoxetine groups had significantly higher risk of appetite loss relative to placebo groups" (p 7). Results were similar for sleep disturbance, and for both sleep and appetite disturbance, "no significant differences between different drug types" were noted (p 8). This corresponds to our finding of greater appetite and sleep disturbances, among other adverse events, among immediate-release methylphenidate-treated patients.

These three meta-analyses, although primarily comparing different types of medication for ADHD-not methylphenidate versus placebo-support the use of immediate-release methylphenidate as an effective treatment for ADHD.

Recently, several randomized, placebo-controlled trials of long-acting methylphenidate in adults with ADHD have been published (Biederman 2006b; Medori 2008; Adler 2009). These trials used OROS methylphenidate, which is an extended-release formulation found to be effective in the treatment of adults with ADHD, with rates of response similar to that seen in the studies included in this review. Because of the different mode of delivery of OROS methylphenidate, we did not include the results of these studies in our review. However, they lend support to our conclusion that immediate-release methylphenidate is effective in treating adults with ADHD.

Regarding dosing, studies have claimed that higher rather than lower doses are more efficacious for the treatment of adults with ADHD (Wilens 2003); investigators have reported a dose-related decrease in ADHD symptoms in response to higher doses of immediate-release methylphenidate (Wilens 1996; Spencer 2001). Our present "high dose-low dose" subgroup analysis does not support these findings. However, it should be stressed again that the studies included in this subgroup analysis had relatively small sample sizes.

AUTHORS' CONCLUSIONS

Implications for practice

Available data from randomized controlled trials suggest that immediate-release methylphenidate is efficacious in treating adults diagnosed with ADHD. Although no adverse effects of a serious clinical nature were noted, because the data regarding safety were not reported in a systematic way, it was not possible to conduct

a meta-analysis of adverse effects. The main adverse effect noted in the included studies was loss of appetite with, in some cases, weight loss. As the prevalence of ADHD among adults suffering from obesity is higher than in the general population (Altfas 2002; Davis 2006), the adverse effect of weight loss seen with immediate-release methylphenidate might be advantageous among people suffering from both ADHD and obesity. The results of this review cannot show whether this weight loss continues over time, or if this side effect is transient and more pronounced during the first stages of treatment, as may be the case with selective serotonin reuptake inhibitors (SSRIs) (Sussman 2001). In any event, based on the evidence, it is advisable to monitor appetite and weight, especially during early phases of treatment.

Implications for research

Although the quality of the body of evidence in this review is generally high, it is our conclusion that larger and especially longer studies are needed to assess the efficacy of immediate-release methylphenidate treatment in adults diagnosed with ADHD. We believe this to be so because some outcomes, such as overall change, general mental state changes, and assessment of functioning, may require a longer study duration for changes to be noted, and longer duration of studies may elucidate the course and clinical relevance of other adverse effects such as loss of appetite and weight.

Another deficit revealed in this review is the lack of uniformly accepted, standardized outcome measurements. This is due, in part, to the fact that our included studies span three decades, although more recent studies also did not show a tendency toward standardized assessments. The use of uniformly accepted scales, analogous to the Positive and Negative Syndrome Scale in schizophrenia, will be helpful in pooling results across studies.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bouffard 2003

Methods	Study design: randomized, placebo-controlled Group design: cross-over Duration of the study: 9 weeks: 2 weeks low dosage, 2 weeks high dosage, 5 days washout, then crossed over
Participants	Age: 17 to 51 years Sample size: 30 participants reported and data for 30 participants analyzed Inclusion criteria: • *DSM-IV* ADHD criteria • 1.5 or higher on an ADHD self-report questionnaire • IQ > 80 Exclusion criteria: psychiatric condition better accounting for current symptoms, substance abuse in the past 6 months, medical CI for stimulants Country: Canada
Interventions	Intervention: immediate-release methylphenidate and placebo Dosage: 3-day lead-in to maximum doses of 10 mg × 3/d to 15 mg × 3/d
Outcomes	Points of evaluation: baseline before trial, midtrial low-dosage evaluation (after 2 weeks) , post high-dosage evaluation (after 4 weeks). Repeated for second trial arm Measured outcomes: • CPT • ○ Omission error rate: ◇ Baseline mean (SD): 4.3 (4.3) ◇ Placebo mean (10 mg): 3.9 (7.6) ◇ Placebo mean (15 mg): 3.7 (8.5) ◇ Medication mean (10 mg): 1.3 (2.1) ◇ Medication mean (15 mg): 1.0 (1.7) ◇ Baseline vs placebo: NS ◇ Baseline vs medication: F = 16.78, P value < 0.0001 ◇ Placebo vs medication: F = 3.75, P value < 0.1 • SCL-90R • Hamilton Anxiety Rating Scale • Beck Depression Inventory • Stop-Signal Test • Adult ADHD Problem Behaviors Rating Scale • Conners Adult ADHD Rating Scale Adverse effects: no significant differences from placebo. Mild to moderate appetite decrease: 41% of immediate-release methylphenidate participants, 23% at baseline; 19% placebo
Notes	• As this was a cross-over trial, and no data were given as to individual arms of the trial, we regarded the trial's endpoint as the endpoint of 2 discrete groups • CPT is an objective, standardized test of attention and response inhibition

Bouffard 2003 (*Continued*)

	• As the level of medication (placebo or immediate-release methylphenidate) had no significant effect on any measure, the results of different dosages were combined • Only medication responses greater than placebo responses were considered

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants gave randomly chosen numbers (picked from a hat) to pharmacist
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described in sufficient detail
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No method of blinding was mentioned, except using a commercially available sugar pill as placebo, which may or may not have been identical in appearance to immediate-release methylphenidate
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	8 participants dropped out after randomization. Reasons for dropout: side effects = 1, not blind to methylphenidate = 4, "too much going on" = 1, unknown reasons = 2. No ITT carried out
Selective reporting (reporting bias)	Low risk	All prestated outcomes were reported
Other bias	Low risk	Study appears to be free of other sources of bias

Gualtieri 1985

Methods	Study design: randomized, placebo-controlled Group design: cross-over Duration of the study: 12 days: 2 × 5-day conditions with a 68-hour washout period
Participants	Age: adults. Specific ages not given Sample size: 8 males. Data not entered into analysis Inclusion criteria: • Current *DSM-III* Attention Deficit Disorder Residual Type (ADD-RT) criteria • Clinical history consistent with ADD in childhood Exclusion criteria: not mentioned Country: USA, North Carolina
Interventions	Intervention: immediate-release methylphenidate and placebo Dosage: 0.3 mg/kg of methylphenidate twice daily at 08:00 and at 12:00

Gualtieri 1985 (*Continued*)

Outcomes	Points of evaluation: baseline before trial, after first drug or placebo administration, and at the end of each condition Measured outcomes: • Baseline before trial: blood pressure, pulse, baseline growth hormone levels • 1 hour after first administration: blood pressure, pulse, growth hormone level, methylphenidate serum level, CPT (with wristwatch actometer) • At the end of each condition: self-report on Adult Activity Scale (AAS), Zung Self-Rating Depression Scale (ZSDS), and Zung Self-Rating Anxiety Scale (ZSAS) • Adverse effects were not specifically reported, but pulse and blood pressure were measured and changes reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information was given about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	No information was given about measures taken for allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	No information was given about measures taken for blinding. All participants were able to accurately guess active drug condition
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts were reported. No outcome data were missing
Selective reporting (reporting bias)	Low risk	All prestated outcomes were reported
Other bias	High risk	• It is not clear on what basis the 8 participants in the short-term efficacy study were selected from the 22 participants included in the initial characterization study • Participants took part in several experimental protocols over a 3-year period. It is not clear how much time passed between initial characterization and recruitment until the efficacy study commenced

Kooij 2004

Methods	Study design: randomized, placebo-controlled Group design: cross-over Duration of the study: 2 × 3-week treatment periods with a 1-week washout period
Participants	Age: 20 to 56 years Sample size: 45 participants reported and data for 45 participants analyzed Inclusion criteria: • Full diagnosis of adult ADHD-*DSM-IV* diagnostic criteria • Childhood diagnosis of ADHD • Chronic persisting course of ADHD from childhood to adulthood • Impairment attributed to ADHD symptoms Exclusion criteria: clinically significant, chronic medical conditions; mental retardation; tic disorder; clinically unstable psychiatric condition; prior use of methylphenidate; pregnant or nursing women Country: Netherlands
Interventions	Intervention: immediate-release methylphenidate and placebo Dosage: week 1 = 0.5 mg/kg, week 2 = 0.75 mg/kg, week 3 = 1 mg/kg
Outcomes	Points of evaluation: at the end of each trial week, not including washout Measured outcomes: • ADHD symptoms-self-report *DSM-IV* ADHD Rating Scale: 13% responded to placebo, 42% to immediate-release methylphenidate (P value 0.011) ◦ Arm 1: MPH mean = 1.37 (SD = 0.65); placebo mean = 1.45 (SD = 0.59) ◦ Arm 2: placebo mean = 1.55 (SD = 0.56); MPH mean = 1.24 (SD = 0.74) • Severity of ADHD as assessed by CGI-ADHD: 18% responded to placebo, 51% to immediate-release methylphenidate (P value 0.011) • ◦ Arm 1: MPH mean = 4.36 (SD 1.47); placebo mean = 5.40 (SD 1.5) ◦ Arm 2: placebo mean = 4.8 (SD 1.47); MPH mean = 4.4 (SD 1.7) • Hamilton Depression Scale • Hamilton Anxiety Scale • Functioning-GAF Outcome definitions: • At least a 2-point decrease on CGI-ADHD scale • 30% or more symptom reduction as measured by self-report *DSM-IV* ADHD Rating Scale Adverse effects (AEs): Only AE to appear significantly more often with MPH than with placebo was loss of appetite (22% vs 4%, P value 0.039)
Notes	• Although this was a cross-over trial, data were given as to individual arms of the trial • In this trial, the only outcome measure addressed was the CGI scale, which, in this trial, is based on self-assessment One of the included papers, Boonstra 2005, provided no clinical assessment of ADHD symptoms

Risk of bias

Bias	Authors' judgement	Support for judgement

Kooij 2004 (*Continued*)

Random sequence generation (selection bias)	Low risk	Order of treatment randomly assigned by computer-generated list
Allocation concealment (selection bias)	Unclear risk	No information regarding allocation concealment was provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Methylphenidate and placebo were dispensed in identically appearing tablets. Medication was prescribed under double-blind conditions
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts were reported. No outcome data were missing
Selective reporting (reporting bias)	Low risk	All prestated outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Kuperman 2001

Methods	Study design: randomized, placebo-controlled Group design: parallel Duration of the study: 1-week, single-blind, placebo lead-in, followed by 7 weeks of placebo, immediate-release methylphenidate or bupropion. Total of 8 weeks
Participants	Age: 18 to 60 years Sample size: 30 participants (MPH = 8 participants, placebo = 11 participants, bupropion = 11 participants). Data reported, entered, and analyzed for 8 participants in immediate-release methylphenidate arm and 11 participants in placebo arm Diagnostic criteria: *DSM-IV* Inclusion criteria: ADHD diagnosis consisting of (1) full *DSM-IV* criteria for ADHD at time of study, (2) chronic course of ADHD symptoms from childhood to adulthood, and (3) moderate or severe level of impairment attributed to ADHD symptoms Exclusion criteria: clinically significant, chronic medical condition; another Axis I diagnosis; unstable psychiatric symptoms; females of reproductive age not on medically approved contraception Country: USA
Interventions	Intervention: immediate-release methylphenidate, bupropion, placebo Dosage: titered over 1 week to maximum dose of 0.9 mg/kg/d in 3 doses
Outcomes	Points of evaluation: baseline and study completion Measured outcome (see note 2): • CGI scale: "very much improved" or "much improved": placebo = 3/11; immediate-release methylphenidate = 4/8 Neuropsychological tests: • Conners Continuous Performance Test

	○ Immediate-release methylphenidate (n = 7) ◇ Baseline = 3.8 ± 1.9 ◇ Change = 0.8 ± 1.9 ○ Placebo = (n = 7): ◇ Baseline = 4.3 ± 1.1 ◇ Change = 0.2 ± 1.1 ○ P value 0.68 • Hamilton Anxiety and Depression Scales • ADHD Symptoms Checklist Severity Scale (ADHDRS-self) • Hopkins Verbal Learning Test • Digit Ordering Test • Trials A and B • Verbal Fluency Test Adverse effects: similar number of complaints between treatment groups; 80% rated mild, 20% moderate Common immediate-release methylphenidate complaints: appetite suppression = 3/12; insomnia, tremor, sweating, jitteriness = 2/12 each Placebo complaints: tiredness = 2/12
Notes	• Compliance was assessed by pill counts and blood measurements for medication levels obtained at end of study • In this trial, the only outcome measure addressed was the CGI scale, which, in this trial, is based on physician assessment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information was given about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	No information was given about measures taken for allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Interventions were administered at the same time, but no mention was made of any other blinding procedures. It is likely that participants were not blinded to their allocated intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	37 participants were enrolled. 5 were dropped before completing the placebo lead-in, and 2 left during the first week of randomized treatment. Thus, 7 participants were dropped before the first week of randomization. 30 were analyzed (11 in MPH, 11 in bupropion SR, and 8 in placebo). Of these, 3 participants indicated their preference for not being at risk for

Kuperman 2001 (*Continued*)

		placebo treatment; 3 withdrew because of complaints of adverse effects (2 on immediate-release methylphenidate and 1 on placebo); and 1 participant was dropped from further participation in the study because of noncompliance with the protocol. These 7 dropouts were analyzed using a "last observation carried forward approach" (LOCF) for participants completing at least 1 week of double-blind treatment. Although an LOCF approach was used, this was applied after 7 dropouts (from the original 37 randomly assigned). Exact numbers per treatment and reasons were not given. Exclusion from analysis: participants who withdrew before completion of 1 week of randomized treatment were excluded
Selective reporting (reporting bias)	Low risk	All prestated outcomes were reported
Other bias	Low risk	The study seems to be free of other sources of bias

Mattes 1984

Methods	Study design: randomized, placebo-controlled Group design: cross-over Duration of the study: 3-week trial for each agent, no washout period
Participants	Age: 18 to 45 years Sample size: 26 participants reported in cross-over study. Data entered and analyzed for 26 participants Diagnostic criteria: *DSM-III* Inclusion criteria: score above a mean of 2 on a 4-point scale of typical adult ADD symptoms, with symptoms of restlessness, difficulty concentrating, excitability, impulsivity, and irritability; psychiatric rating of at least 2 on at least 3 of previously mentioned 5 symptoms of adult ADD Exclusion criteria: current substance dependence, schizophrenia, major affective disorder (except major depressive episode of mild severity), psychosis Country: USA
Interventions	Intervention: immediate-release methylphenidate and placebo Dosage: immediate-release methylphenidate started at 5 mg × 2/d for 2 days, increased to 10 mg × 2/d for 2 days, thereafter increased by 10 mg every 2 days to maximum 30 mg × 2/d

Outcomes	Points of evaluation: global improvement weekly. Adult ADD questionnaires (completed by participants) after weeks 3 and 6 Measured outcomes: • Adult ADD questionnaire • SCL-90 • POMS • Structured interview form of 23 ratings of adult ADD symptoms • CPI-California Personality Inventory Adverse effects: Anorexia, headache, and late-afternoon depression appeared significantly more often in the treatment group
Notes	• As this was a cross-over trial, and no data were given as to individual arms of the trial, we regarded the trial endpoint as the endpoint of 2 discrete groups • Responders offered continuation of treatment and were contacted 6 to 12 weeks after study completion. Of 16 responders, 2 were taking immediate-release methylphenidate

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	All participants assessed as having childhood ADHD at varying levels of certainty (probably to definitely) were randomly assigned to a double-blind, placebo-controlled, cross-over study. No information was given regarding sequence generation, and this study was judged as having unclear risk of bias regarding random sequence generation
Allocation concealment (selection bias)	Unclear risk	All participants assessed as having childhood ADHD at varying levels of certainty (probably to definitely) were randomly assigned to a double-blind, placebo-controlled, cross-over study. No information was given regarding allocation concealment. Therefore, this study was judged as having unclear risk of bias regarding allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details were provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Five participants dropped out, balanced across groups (3 from intervention group, 2 from control group); 2 of the drop-outs completed the methylphenidate trial.

Mattes 1984 (*Continued*)

		As this was a cross-over study, we assume that these 2 dropouts dropped out from the placebo arm after completing the methylphenidate arm, but this is unclear. As dropout was balanced across groups, the study was assessed as having unclear risk of bias with regard to Incomplete outcome data
Selective reporting (reporting bias)	High risk	Not all prespecified primary outcomes of the study have been reported
Other bias	Low risk	Study appears to be free of other sources of bias. The fact that no washout period was provided may be assumed to be a source of additional bias. However, points of assessment were measured at the end of each treatment period, that is, 3 weeks after initiation of treatment, making the impact of no washout period negligible. In addition, methylphenidate has a pharmacokinetic half-life of 2 to 3 hours (Kimko 1999), further weakening the effect of no washout period

Spencer 1995

Methods	Study design: randomized, placebo-controlled Group design: cross-over Duration of the study: 3-week medication trial, 1 intervening washout week
Participants	Age: 17 to 51 years Sample size: 25 participants. Data for 23 participants reported and analyzed, as 2 participants dropped out Inclusion criteria: • *DSM III-R* ADHD criteria • 1.5 or greater on ADHD self-report questionnaire • IQ > 80 Exclusion criteria: • No psychiatric condition better accounting for current symptoms • No substance abuse for 6 months • No medical CI for stimulants Exclusion criteria: clinically significant medical conditions; abnormal laboratory values; tic disorder; mental retardation; unstable psychiatric conditions; substance abuse or dependence in prior 6 months; use of psychotropics; pregnant or nursing women Country: Massachusetts, USA

Spencer 1995 (*Continued*)

Interventions	Intervention: immediate-release methylphenidate or placebo Dosage: medication titered to 0.5 mg/kg/d by week 1, 0.75 mg/kg/d by week 2, up to 1 mg/kg/d by week 3
Outcomes	Points of evaluation: baseline, at end of each week Measured outcomes: • ADHD, Depression and Anxiety assessed by Clinical Global Impression Scale (CGI): placebo = 1/23, immediate-release methylphenidate = 18/23 • ADHD Rating Scale (14 ADHD criteria symptoms) (see notes 4 and 5): • ○ Hyperactivity: placebo mean = 1.88, SD = 0.95; immediate-release methylphenidate mean = 0.84, SD = 0.95 ○ Impulsivity: placebo mean = 1.99, SD = 0.95; immediate-release methylphenidate mean = 0.91, SD = 0.48 ○ Inattentiveness: placebo mean = 2.28, SD = 0.48; immediate-release methylphenidate mean = 1.89, SD = 0.48 • Hamilton Anxiety Scale • Hamilton Depression Scale Adverse effects: 13% not able to tolerate target dose of 1 mg/kg/d. Subjective adverse effect rate on medication similar to that on placebo Common adverse effects: loss of appetite = 6/23, insomnia and anxiety = 5/23 each
Notes	• As this was a cross-over trial, and no data were given as to individual arms of the trial, we regarded the trial endpoint as the endpoint of 2 discrete groups • No participant previously treated • Rating based on physician's assessment • We converted standard error to standard deviation using the formula: SE = SD/n • No follow-up reported after end of study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information about the sequence generation was insufficient to permit judgement
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described in sufficient detail to allow a definitive judgement
Blinding (performance bias and detection bias) All outcomes	Low risk	Active drug and placebo dispensed in identical 5-mg and 10-mg capsules; medication prescribed under double-blind conditions
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 participants dropped out of intervention group because of adverse effects and were not included in the analysis
Selective reporting (reporting bias)	Low risk	All prestated outcomes were reported

Spencer 1995 (*Continued*)

Other bias	Low risk	Study appears to be free of other sources of bias

Spencer 2005

Methods	Study design: randomized, placebo-controlled Group design: parallel Duration of the study: 6 weeks
Participants	Age: 17 to 51 years Sample size: 146 participants (104 participants in immediate-release methylphenidate arm and 42 participants in placebo arm). Data reported, entered, and analyzed for 146 participants Inclusion criteria: • *DSM-IV* ADHD criteria • Full criteria met by the age of 7 and in the last month • Chronic course of ADHD • Moderate to mild functional impairment All of the above by interview and clinical diagnosis Exclusion criteria: chronic, clinically significant medical condition; dementia; delirium; abnormal laboratory values; memory impairment; IQ < 80; unstable psychiatric condition; prior, satisfactory use of immediate-release methylphenidate Country: Massachusetts, USA
Interventions	Intervention: immediate-release methylphenidate and placebo Dosage: titered up to 0.5 mg/kg/d by week 1, 0.75 mg/kg/d by week 2, 1 mg/kg/d by week 3. Maximum of 1.3 mg/kg by weeks 5 and 6
Outcomes	Points of evaluation: weekly. Except HAM-A, HAM-D, and BDI-evaluated at beginning and end of study Measured outcomes (by board certified or board eligible psychiatrist): • Severity and change in severity of ADHD as assessed by CGI-ADHD • Specific ADHD symptoms assessed by AISRS-Adult ADHD Investigator System Report Scale • Depressive symptoms-Hamilton Depression Scale and Beck Depression Inventory • Anxiety-Hamilton Anxiety Scale Response: 30% reduction in AISRS; "much" or "very much" improved in CGI Adverse effects: appetite suppression, dry mouth, mild moodiness for treatment group
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information about the sequence generation process was insufficient to permit judgement. Participants were randomly assigned

Spencer 2005 (*Continued*)

		to MPH or placebo at a ratio of 2.5:1
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described in sufficient detail
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of participants and study personnel was ensured. Weekly supplies of MPH or placebo were dispensed by the pharmacy in identically appearing 5-mg and 10-mg capsules
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts: 10 before completion of 2 weeks of treatment, 26 before trial completion. Dropout rate did not differ between medication and placebo (25% (26/104) vs 24% (10/42)). Of reasons for dropout, only "no effect" was important. Exclusion from analysis: yes, but dropout did not differ between groups (25% MPH vs 24% placebo)
Selective reporting (reporting bias)	High risk	Not all assessed data were reported
Other bias	Low risk	Study appears to be free of other sources of bias

Tenenbaum 2002

Methods	Study design: randomized, placebo-controlled Group design: cross-over Duration of the study: 14 to 17 weeks (3 weeks for each condition-pycnogenol, methylphenidate, placebo), 1-week washout between conditions, 1-week baseline, 3- to 4-week follow-up)
Participants	Age: 24 to 53 years Sample size: 33 participants entered the study; 24 completed the study and data were entered into the analysis (except for 1 subscale for which data were reported and entered for 23 participants). 9 participants dropped out Inclusion criteria: *DSM-IV* ADHD combined type criteria Exclusion criteria: clinically significant medical condition; active substance abuse (and 6 months before); pregnant or nursing females; prescribed psychoactive medication Country: USA
Interventions	Intervention: immediate-release methylphenidate, placebo, pycnogenol Dosage: methylphenidate titered within 8 to 10 days to 10 mg × 3/d, and within 14 days to 15 mg × 3/d

Tenenbaum 2002 (*Continued*)

Outcomes	Points of evaluation: 5-baseline, at end of each condition, and at follow-up Measured outcomes: • Barkley's ADHD Scale (subscales of inattention and hyperactivity or impulsivity) • ADSA (Attention Deficit Scales for Adults) • Barrett Impulsiveness Scale • Beck Depression Inventory • Beck Anxiety Inventory • Copeland Symptoms Checklist for Adult Attention Deficit Disorders • Brown ADD scales • Conners CPT Adverse effects: no reference to adverse effects. (We cannot say whether this was so because no adverse effects occurred, or because no measures were taken to record adverse effects.)
Notes	• As this was a cross-over trial, and no data were given as to individual arms of the trial, we regarded the trial endpoint as the endpoint of 2 discrete groups • All measured outcomes (except CPT) were participant (i.e. self) rated or rated by significant others .

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information about the sequence generation process was insufficient to permit judgement
Allocation concealment (selection bias)	Unclear risk	Information was insufficient to permit judgement
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of participants and study personnel was described. Medication and placebo were dispensed in identical tablets, 4 times daily
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9 participants discontinued because of noncompliance with medication or appointments. No information is given as to their group of assignment and why they were not compliant. Baseline scores of completers vs noncompleters were compared, with no important difference noted. Exclusion from analysis: no data given. No significant difference between those who complied and those who did comply at baseline
Selective reporting (reporting bias)	Low risk	All prestated outcomes were reported

Tenenbaum 2002 (*Continued*)

Other bias	Unclear risk	Information was insufficient to assess whether an important risk of bias exists

Wender 1985

Methods	Study design: randomized, placebo-controlled . Group design: cross-over Duration of the study: 2-week trial of placebo and immediate-release methylphenidate with 1-week intervening washout period. No follow-up past 5-week study period
Participants	Age: 21 to 45 years Sample size: 37 participants; data reported, entered, and analyzed for 37 participants Diagnostic criteria: *DSM-III* Inclusion criteria: all of the following: • Childhood ADHD • Persistence of hyperactivity and attention deficit • Two of the following: affective lability, inability to complete tasks, explosive temper, impulsivity, stress intolerance. • Clinical symptoms: impulsivity, irritability, restlessness, and emotional lability Exclusion criteria: psychiatric comorbidities Country: Salt Lake City area, Utah, USA
Interventions	Intervention: immediate-release methylphenidate and placebo Dosage: 5 mg at 8:00 am and noon, increased by 5 mg per dose every 2 to 3 days. Maximum dose 30 mg × 3
Outcomes	Points of evaluation: every week, starting at t = 0, a total of 6 measurements Measured outcomes: • Physician Target Symptoms Scale • Physician Global Rating Scale • Medicine response sheet (participant's subjective experience) • Global Assessment Scale • POMS • SCL-90 Adverse effects: 11 participants (30%) reported adverse effects; 8 while only on immediate-release methylphenidate
Notes	• As this was a cross-over trial, and no data were given as to individual arms of the trial, we regarded the trial endpoint as the endpoint of 2 discrete groups • Although initially, study authors required participants without psychiatric comorbidities, they report that the sample contained many participants who met other *DSM-III* criteria: dysthymic disorder (68%), cyclothymic disorder (22%), and generalized anxiety disorder (11%)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Wender 1985 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	No information about the sequence generation process was provided to permit judgement
Allocation concealment (selection bias)	Unclear risk	Information was insufficient to permit judgement
Blinding (performance bias and detection bias) All outcomes	Low risk	Medication and placebo were dispensed in identical tablets
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information was given as to dropouts
Selective reporting (reporting bias)	Low risk	All prestated outcomes were reported
Other bias	Unclear risk	Information was insufficient to permit assessment of whether an important risk of bias exists

Wender 2011

Methods	Study design: randomized, placebo-controlled Group design: cross-over Duration of the study: 1 week, single-blind, run-in on placebo, followed by a 2-week periods of placebo or immediate-release methylphenidate, each with no clear washout period. 1-year follow-up for responders
Participants	Age: 21 to 55 years Sample size: 116 participants entered, data analyzed for 105 participants because 11 participants dropped out Inclusion criteria: Utah Criteria for ADHD • All of the following: ◦ Childhood ADHD ◦ 95th percentile on Parents' Rating Scale or the Wender Utah Rating Scale ◦ Diagnosis of ADHD in adulthood based on Utah criteria Exclusion criteria: other Axis I or II diagnosis Country: Salt Lake City area, Utah, USA
Interventions	Interventions: immediate-release methylphenidate and placebo Participants started on 10 mg, 3 times a day, up to a maximum dose of 60 mg/d Average final dose was 45 ± 14 mg/d of immediate-release methylphenidate at the end of the immediate-release methylphenidate arm
Outcomes	Symptoms of ADHD assessed by: • WRAADDS (Wender-Reimherr Adult Attention Deficit Disorder Scale)-a clinician-administered structured interview that evaluates the 7 symptoms of the Utah Criteria

	• CGI These were administered at baseline and at the end of each 2-week condition • Social functioning was measured by the Weissman Social Adjustment Scale (WSAS) • Overall functioning was assessed using Global Assessment of Functioning (GAF) • Adverse events were reported
Notes	As this was a cross-over trial, and no data were given as to individual arms of the trial, we regarded the trial endpoint as the endpoint of 2 discrete groups

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information about sequence generation process was given to permit judgement. Randomization was determined by a random number table
Allocation concealment (selection bias)	Unclear risk	No information was provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Implemented by the clinic's study facilitator, while staff involved in treatment or evaluation remained blinded to assignment. No means of ensuring blinding was described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	11 of 116 dropped out before completion of double-blind trial (9.5%). No information was given with regard to reasons for dropout or the arm from which they were dropped. No direct information is given as to dropout inclusion in analysis, but data regarding adverse events and vital signs were given for 105 participants only
Selective reporting (reporting bias)	Low risk	Prestated outcomes were reported, not all of them (GAF, for example) for the short-term trial
Other bias	Unclear risk	Information was Insufficient to permit assessment of whether an important risk of bias exists The fact that no washout period was provided may be assumed to be a source of additional bias. However, methylphenidate has a pharmacokinetic half-life of 2 to 3 hours, weakening the effect of no washout period. In addition, the author's

		note that "no interaction between outcome and either dose or treating physician were identified" (p 40) and that "there was an order effect such that after receiving methylphenidate placebo response was significantly reduced (P value = 0.037). The treatment response during just the first double-blind period remained statistically significant and clinically impressive" (p 40). Methylphenidate has been repeatedly found to be susceptible to identification by participants in double-blind studies. Therefore, we do not think that lack of a washout period constitutes a significant additional source of bias in this trial

Wood 1976

Methods	Study design: randomized, placebo-controlled Group design: cross-over Duration of the study: 4 weeks = 2 × 2-week periods of placebo and immediate-release methylphenidate with no washout period
Participants	Age: 21 to 60 years Sample size: 11 participants. Data reported, entered, and analyzed for 11 participants Diagnostic criteria: Minimal Brain Dysfunction (MBD) *DSM-II* Health status: All participants were diagnosed with at least 1 other psychiatric disorder Inclusion criteria: • Clinical symptoms of Impulsivity, irritability, restlessness, emotional lability • Long-standing history of impulsiveness, inattentiveness, short temper, emotional lability • Retrospective diagnosis of minimal brain dysfunction in childhood Participants chosen were above the 95th percentile per parent report Exclusion criteria: diagnosed with schizophrenia, affective disorder, mental retardation, or organic brain syndrome Country: Salt Lake City area, Utah, USA
Interventions	Intervention: immediate-release methylphenidate or placebo Dosage: twice daily, variable dosage schedule, starting at 20 mg/d to maximum 60 mg/d
Outcomes	Points of evaluation: baseline and at end of each drug condition Measured outcomes: 7-point, 5-dimension scale (maximum of 35 points) participant report = "nervous-calm," "energetic-tired," "mind wandering-concentrating well," "hot tempered-cool tempered," and "happy-sad" Adverse effects: no mention of adverse effects (measured or described)
Notes	• As this was a cross-over trial, and no data were given as to individual arms of the trial, we regarded the trial endpoint as the endpoint of 2 discrete groups • Following the double-blind, cross-over trial, each of the 11 participants received

Wood 1976 (*Continued*)

	an open trial of pemoline or TCA, or both	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information about sequence generation process was provided to permit judgement
Allocation concealment (selection bias)	Unclear risk	No information was given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No means of ensuring blinding was described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts were reported
Selective reporting (reporting bias)	Low risk	All prestated outcomes were reported
Other bias	Unclear risk	Information was insufficient to permit assessment of whether an important risk of bias exists The fact that no washout period was provided may be assumed to be a source of additional bias. However, methylphenidate has a pharmacokinetic half-life of 2 to 3 hours, weakening the effect of no washout period

AE: adverse effects.
AAS: Adult Activity Scale.
ADD: attention deficit disorder.
ADD-RT: attention deficit disorder residual type.
ADHD: attention deficit hyperactivity disorder.
ADSA: Attention Deficit Scales for Adults.
AISRS: Adult Investigator System Report Scale.
ASRS: Adult ADHD Self-Report Scale.
CGI: Clinical Global Impression Scale.
CI: confidence interval.
CPI: California Personality Inventory.
CPT: Continuous Performance Test.
DSM-II: Diagnostic and Statistical Manual of Mental Disorders, Second Edition.
DSM-III: Diagnostic and Statistical Manual of Mental Disorders, Third Edition.
DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised.
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.
GAF: Global Assessment of Functioning.
LOCF: last observation carried forward.

MBD: minimal brain dysfunction.
MPH: methylphenidate.
NS: not significant.
POMS: Profile of Mood States.
SCL-90: Symptom Checklist 90.
SCL-90R: Symptom Checklist 90, revised.
SD: standard deviation.
SE: standard error.
TCA: tricyclic antidepressant.
WRAADDS: Wender-Reimherr Adult Attention Deficit Disorder Scale.
WSAS: Weissman Social Adjustment Scale.
ZSAS: Zung Self-Rating Anxiety Scale.
ZSDS: Zung Self-Rating Depression Scale.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Faraone 2001

Methods	No information
Participants	No information
Interventions	No information
Outcomes	No information
Notes	This conference presentation probably refers to a published meta-analysis by the same name: Adderall and methylphenidate in ADHD (Faraone SV, Biederman J, Roe CJ. Comparative efficacy of Adderall and methylphenidate in attention-deficit/hyperactivity disorder: a meta-analysis.Clinical Psychopharmacology 2002 Oct;22(5):468-73). We contacted the study author. His kind reply stated that all of his work on this topic has been published

Perry 2000

Methods	No information
Participants	Adults with ADHD
Interventions	Bupropion sustained-release, methylphenidate, and placebo
Outcomes	No information
Notes	We think this relates to our included study-Kuperman 2001-but the study authors did not reply to our email inquiring about this

Perry 2002

Methods	No information was provided
Participants	Adults with ADHD
Interventions	Bupropion sustained-release, methylphenidate, and placebo
Outcomes	No information was provided
Notes	We think this relates to our included study-Kuperman 2001-but the study authors did not reply to our email inquiring about this

Spencer 2003

Methods	Double-blind, nonrandomized, stability of response study
Participants	Adults with ADHD
Interventions	Methylphenidate
Outcomes	Symptoms of ADHD
Notes	This report is a continuation study (phase 2) of a probably included study (Spencer 2005-phase 1). In this experiment, responders to phase 1 were continued to a double-blind maintenance study assessing stability of response: • We contacted study authors regarding this report but received no reply • In our search, we did not find a published study of this report • Because this experiment was not randomized (included only those defined as responders-59 to methylphenidate and 6 to placebo), we would not have been able to include it in any case

Wender 2001b

Methods	No Information was provided
Participants	Adults with ADHD
Interventions	Methylphenidate
Outcomes	No information was given
Notes	We contacted the study author and received a reply that the presentation dealt with new data, which, at the time, were unpublished. During the course of preparation of the review, a study was published that was subsequently included (Wender 2011). We think it highly likely that Wender 2011 contains the aforementioned previously unpublished data presented at the conferences. We contacted Paul H. Wender again after completing our updated search to confirm this but received no reply

Wender 2002

Methods	No Information was given
Participants	Adults with ADHD
Interventions	Methylphenidate
Outcomes	No information
Notes	We contacted the study author and received a reply that the presentation dealt with new data, which, at the time, was unpublished. During the course of preparation of the review, a study was published that was subsequently included (Wender 2011). We think it highly likely that Wender 2011 contains the aforementioned previously unpublished data presented at the conferences. We contacted Paul H. Wender again after our updated search to confirm this but received no reply

Wender 2003

Methods	No Information was given
Participants	Adults with ADHD
Interventions	Methylphenidate
Outcomes	No information was given
Notes	We contacted the study author and received a reply that the presentation dealt with new data, which, at the time, were unpublished. During the course of preparation of the review, a study was published that was subsequently included (Wender 2011). We think it highly likely that Wender 2011 contains the aforementioned previously unpublished data presented at the conferences. We contacted Paul H. Wender again after our updated search to confirm this but received no reply

ADHD: attention deficit hyperactivity disorder.

DATA AND ANALYSES

Comparison 1. Immediate-release methylphenidate vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall hyperactivity	6	490	Std. Mean Difference (Random, 95% CI)	-0.60 [-1.11, -0.09]
2 Overall impulsivity	5	414	Std. Mean Difference (Random, 95% CI)	-0.62 [-1.08, -0.17]
3 Overall inattentiveness	7	636	Std. Mean Difference (Random, 95% CI)	-0.66 [-1.02, -0.30]
4 Low dose	4		Std. Mean Difference (Random, 95% CI)	Subtotals only
4.1 Hyperactivity	4	354	Std. Mean Difference (Random, 95% CI)	-0.61 [-1.41, 0.19]
4.2 Impulsivity	3	278	Std. Mean Difference (Random, 95% CI)	-0.62 [-1.32, 0.08]
4.3 Inattentiveness	4	354	Std. Mean Difference (Random, 95% CI)	-0.84 [-1.44, -0.25]
5 High dose	3		Std. Mean Difference (Random, 95% CI)	Subtotals only
5.1 Inattentiveness	3	282	Std. Mean Difference (Random, 95% CI)	-0.44 [-0.79, -0.10]
5.2 Hyperactivity	2	136	Std. Mean Difference (Random, 95% CI)	-0.63 [-1.49, 0.23]
5.3 Impulsivity	2	136	Std. Mean Difference (Random, 95% CI)	-0.76 [-1.92, 0.40]
6 Overall change	9	745	Std. Mean Difference (Random, 95% CI)	-0.72 [-1.12, -0.32]
6.1 Continuous data	7	680	Std. Mean Difference (Random, 95% CI)	-0.62 [-1.03, -0.21]
6.2 Dichotomous data	2	65	Std. Mean Difference (Random, 95% CI)	-1.45 [-3.28, 0.38]

Analysis 1.1. Comparison 1 Immediate-release methylphenidate vs placebo, Outcome 1 Overall hyperactivity.

Review: Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 1 Immediate-release methylphenidate vs placebo

Outcome: 1 Overall hyperactivity

Study or subgroup	Treatment N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Wood 1976	11	11	-1.3766 (0.6965)		8.3 %	-1.38 [-2.74, -0.01]
Wender 1985	37	37	-0.92 (0.25)		17.3 %	-0.92 [-1.41, -0.43]
Spencer 1995	23	23	-1.09 (0.24)		17.6 %	-1.09 [-1.56, -0.62]
Tenenbaum 2002	24	24	0.39 (0.19)		18.6 %	0.39 [0.02, 0.76]
Kooij 2004	45	45	-0.21 (0.14)		19.5 %	-0.21 [-0.48, 0.06]
Wender 2011	105	105	-0.8883 (0.1864)		18.7 %	-0.89 [-1.25, -0.52]
Total (95% CI)	**245**	**245**			**100.0 %**	**-0.60 [-1.11, -0.09]**

Heterogeneity: $Tau^2 = 0.32$; $Chi^2 = 40.39$, df = 5 (P<0.00001); $I^2 = 88\%$

Test for overall effect: Z = 2.32 (P = 0.020)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Immediate-release methylphenidate vs placebo, Outcome 2 Overall impulsivity.

Review: Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 1 Immediate-release methylphenidate vs placebo

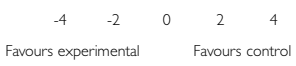
Outcome: 2 Overall impulsivity

Study or subgroup	Treatment N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Wood 1976	11	11	-1.409 (0.5732)		10.6 %	-1.41 [-2.53, -0.29]
Spencer 1995	23	23	-1.4243 (0.4185)		15.1 %	-1.42 [-2.24, -0.60]
Tenenbaum 2002	23	23	0.0476 (0.2951)		20.0 %	0.05 [-0.53, 0.63]
Kooij 2004	45	-0.23139 (0.08607143)	45		28.4 %	-0.23 [-0.40, -0.06]
Wender 2011	105	105	-0.7819 (0.1589)		25.9 %	-0.78 [-1.09, -0.47]
Total (95% CI)	**207**	**207**			**100.0 %**	**-0.62 [-1.08, -0.17]**

Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 20.93$, df = 4 (P = 0.00033); $I^2 = 81\%$

Test for overall effect: Z = 2.68 (P = 0.0074)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Immediate-release methylphenidate vs placebo, Outcome 3 Overall inattentiveness.

Review: Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 1 Immediate-release methylphenidate vs placebo

Outcome: 3 Overall inattentiveness

Study or subgroup	Treatment N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Wood 1976	11	11	-1.4601 (0.6319)		6.1 %	-1.46 [-2.70, -0.22]
Wender 1985	37	37	-1.0958 (0.3241)		12.9 %	-1.10 [-1.73, -0.46]
Spencer 1995	23	23	-0.8132 (0.3402)		12.4 %	-0.81 [-1.48, -0.15]
Tenenbaum 2002	24	24	-0.0226 (0.2887)		14.0 %	-0.02 [-0.59, 0.54]
Kooij 2004	45	-0.20385 (0.11716837)	45		19.7 %	-0.20 [-0.43, 0.03]
Spencer 2005	104	-0.57032552 (0.18584631)	42		17.6 %	-0.57 [-0.93, -0.21]
Wender 2011	105	105	-1.0714 (0.1932)		17.3 %	-1.07 [-1.45, -0.69]
Total (95% CI)	**349**	**287**			**100.0 %**	**-0.66 [-1.02, -0.30]**

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 24.54$, df = 6 (P = 0.00041); $I^2 = 76\%$

Test for overall effect: Z = 3.58 (P = 0.00034)

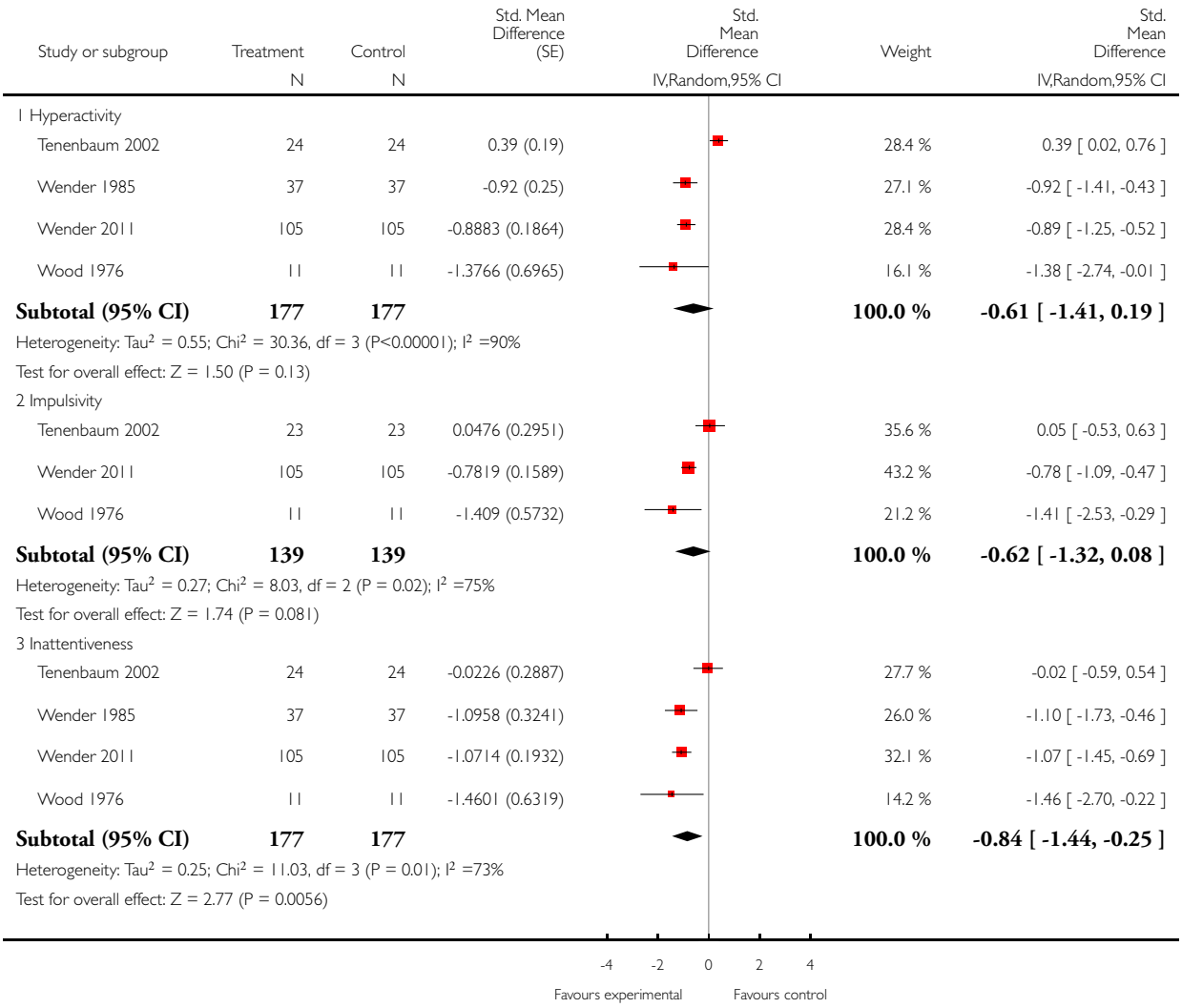
Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Immediate-release methylphenidate vs placebo, Outcome 4 Low dose.

Review: Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 1 Immediate-release methylphenidate vs placebo

Outcome: 4 Low dose

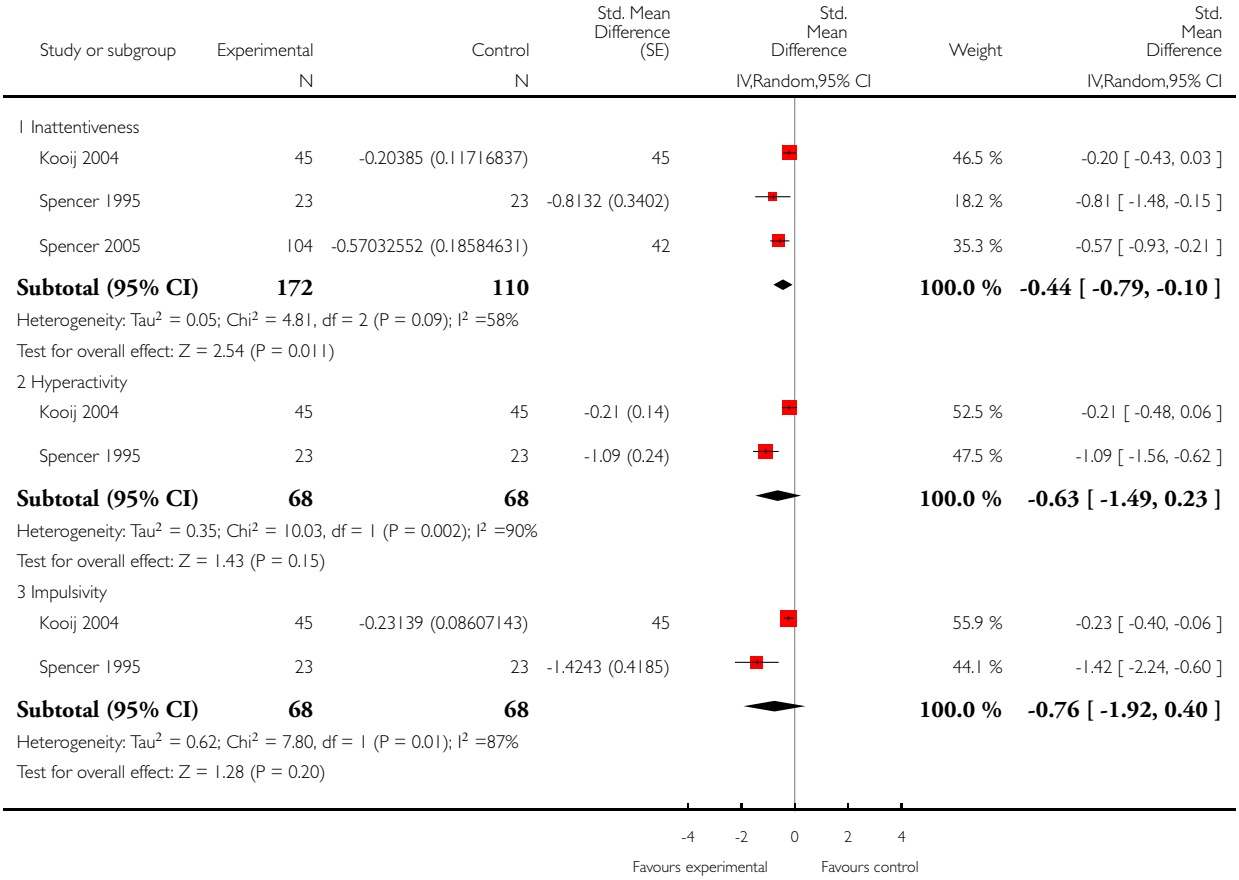


Analysis 1.5. Comparison 1 Immediate-release methylphenidate vs placebo, Outcome 5 High dose.

Review: Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 1 Immediate-release methylphenidate vs placebo

Outcome: 5 High dose

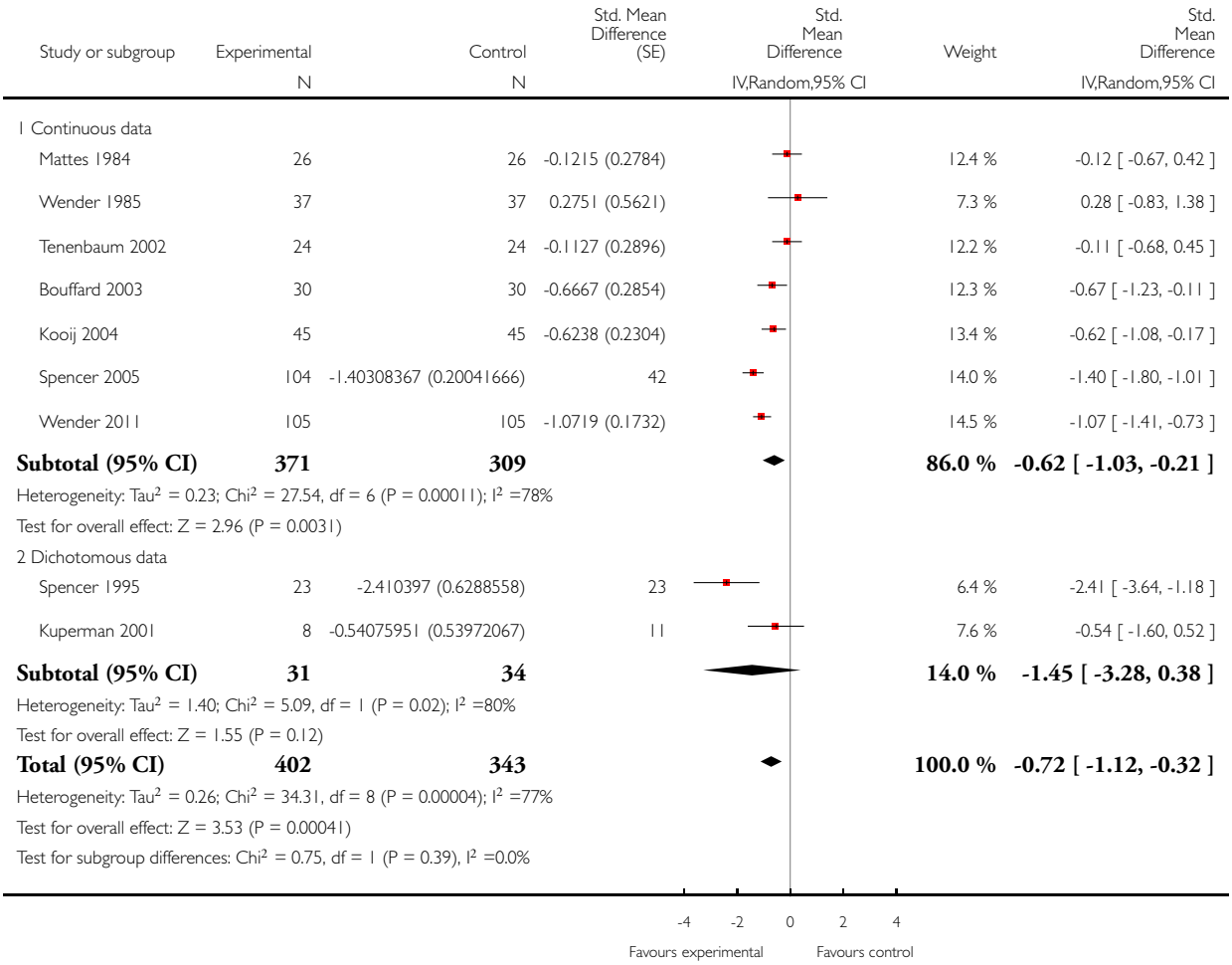


Analysis 1.6. Comparison 1 Immediate-release methylphenidate vs placebo, Outcome 6 Overall change.

Review: Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults

Comparison: 1 Immediate-release methylphenidate vs placebo

Outcome: 6 Overall change



ADDITIONAL TABLES

Table 1. Scales by outcome by study

	Primary outcome: specific ADHD symptoms	Secondary outcome: overall change (continuous data)	Secondary outcome: overall change (binary data)
Wood 1976	Self-rated, non-validated, 7-point scale (higher = worse).	No data.	No data.
Mattes 1984	No data.	Physician-rated, non-validated, 8-point scale (higher = worse)	No data.
Gualtieri 1985	No data.	AAS (Adult Activity Scale). 14-item based on Connors Parent/Teacher questionnaire. Non-validated, self-report scale	No data.
Wender 1985	Physican's target symptom rating. Physician-rated, non-validated, 4-point scale (higher = worse)	Physicians' Global Rating Scale, 7-point (not referenced) or Global Assessment (referenced 1976) both physician-rated (higher = better).	Physician Global Rating Scale - physician-rated, non-validated scale. Responders = moderate to marked treatment response (7-point), higher = better
Spencer 1995	ADHD Rating Scale. Probably physician-rated, 4-point, validated scale (higher = worse)	No data.	Responders = CGI greater than 2 + 30% reduction in individual rating scales
Kuperman 2001	No data.	ADHDRS (ADHD Symptom Checklist Severity), self-rated, (higher = worse)	CGI - clinician-rated. Responders = CGI improvement score of 1 or 2 (higher = worse)
Tenenbaum 2002	1. Barkley's ADHD Rating Scale - 2 subscales, 'inattention' and 'hyperactive/impulsive'. 2. ADSA - 3 subscales, 'attention', 'behavior disorganized', 'emotive' 3. Copeland - 3 subscales for 'inattention', 'impulsivity', 'activity'. 4. Barrat Impulsiveness Scale (subscales given, all refer to impulsiveness). 5. Brown Attention Deficit Disorder Scale (subscales given, all refer to attention).	1. Barkley's ADHD Rating Scale (data for 'overall' and for 'inattention' and 'hyperactivity' or 'impulsivity' subscales). 2. Attention deficit scale for adults (data for 'overall' and for 'attention' subscale). 3. Copeland Symptom Checklist for Adult ADD (data for 'overall' and for 'attention', 'impulsivity', 'hyperactivity' subscales).	No data.
Bouffard 2003	No data.	1. Adult Behavior Scale. 2. Conners' Rating Scale. Both self-report and validated.	Response defined as subjects who improved on methylphenidate more than on placebo and scored

Table 1. Scales by outcome by study (*Continued*)

			less than 1.5 on at least 1 self-report questionnaire. 63% responders
Kooij 2004	Raw data provided by author.	1. CGI - physician-rated. 2. DSM-IV - ADHD rating Scale, validated, self-report.	1. CGI - physician-rated, 18% placebo, 51% MPH. 2. DSM - IV ADHD rating scale, self report: 13% placebo, 42% MPH 3. Combined CGI + ADHD rating scale: 7% placebo, 38% MPH Response: 2-point decrease on CGI + 30% reduction on ADHD rating scale
Spencer 2005	ADHD Rating Scale. Validated, physician-rated (higher = worse). Data extrapolated from graph	ADHD Rating Scale. Validated, physician-rated (higher = worse)	Responders = CGI greater than 2 + 30% reduction AISRS.
Wender 2011	WRAADDS with subscales for attention difficulties, hyperactivity, and impulsivity	Total score WRAADDS.	WRAADDS - percent of patients experiencing at least a 50% reduction of total WRAADDS score

AAS - Adult Activity Scale.
ADD - attention deficit disorder.
ADHD - attention deficit hyperactivity disorder.
ADSA - Attention Deficit Scales for Adults.
CGI - clinical global impression.
DSM-IV - Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.
MTH - methlyphenidate.
WRAADDS - Wender-Reimherr Adult Attention Deficit Disorder Scale.

Table 2. Trial authors contacted

Report or study	Reasons for contact	Reply
Bupropion sustained release versus methylphenidate versus placebo in the treatment of adult ADHD, Perry PJ, GR Gaffney (2000), 153rd Annual Meeting of the American Psychiatric Association (Perry 2000). And, by the same title, at the 155th Annual Meeting of the American Psychiatric Association; 2002 May 18-23rd; Philadelphia, PA (Perry 2002)	We contacted Paul J. Perry to verify if this was a presentation of the data used in Kuperman's article, in which he is a co-author or whether new data was presented	No reply.

Table 2. Trial authors contacted (*Continued*)

A placebo-controlled, long-term trial of methylphenidate in the treatment of adults with ADHD, Wender Paul H, 2001 Annual Meeting of the American Psychiatric Association; 2001 May 5-10; New Orleans; LA, USA (Wender 2001). Other presentations with the same title and by the same speaker were given at the 155th Annual Meeting of the American Psychiatric Association; 2002 May 18-23rd; Philadelphia, PA, USA (Wender 2002) and in the 156th Annual Meeting of the American Psychiatric Association, May 17-22, 2003, San Francisco (Wender 2003)	We contacted Paul H. Wender to request presentation content and additional or unpublished information from included studies	We received a reply that the presentation dealt with new data which, at the time, was unpublished. During the course of preparing this review, a study was published that was subsequently included (Wender 2011). We assume that this study contains the aforementioned previously unpublished data presented in the conferences. We contacted Paul H. Wender again after our updated search but received no reply
Adderall and methylphenidate in ADHD, Faraone SV, Biederman J. 2001 Annual Meeting of the American Psychiatric Association; 2001 May 5-10; New Orleans; LA, USA (Faraone 2001)	We contacted Faraone SV with a request for presentation content	We received his kind reply that all his work on this topic has been published
Preliminary results of a six-month trial of methylphenidate in adults with ADHD, Spencer, T. J. (2003), 156th Annual Meeting of the American Psychiatric Association, May 17-22, San Francisco CA: No. 54B (Spencer 2003)	We contacted TJ Spencer with a request for presentation content	No reply.
Wood 1976	Request for ad.ditional information	No reply.
Mattes 1984	Request for additional information.	No reply.
Gualtieri 1985	Request for additional information.	No reply.
Spencer 1995	Request for additional information.	No reply.
Kuperman 2001	Request for additional information.	No reply.
Tenenbaum 2002	Request for additional information.	Relevant information provided.
Bouffard 2003	Request for additional information.	No reply.
Kooij 2004	Raw data as to the numbers of specific questions in questionnaire used to identify patient status regarding the three subsets and what improvement regarding said subsets was measured, enabling us to clearly outline not only general improvement but also	Requested information received in full.

Table 2. Trial authors contacted (*Continued*)

	specific improvement	
Spencer 2005	Request for additional information.	No reply.

Table 3. Dropouts

Study	Dropout Rate	Comments
Wood 1976	No dropouts reported.	
Mattes 1984	7.5% 5 / 66	No ITT analysis. 5 participants dropped out, balanced across groups (3 from intervention group, 2 from control group), 2 of the dropouts completed methylphenidate trial
Gualtieri 1985	No dropouts reported.	
Wender 1985	No dropouts reported.	
Spencer 1995	8% 2 / 25	No ITT analysis. 2 participants dropped out: 1 - due to chest pain, 1 - due to irritability. Both dropouts from immediate-release methylphenidate group
Kuperman 2001	19% 7 / 37	ITT analysis conducted for all completers of first week post randomization. Participants who withdrew prior to 1 week completion of randomised treatment excluded from analysis 5 participants dropped out prior to completing the placebo lead-in and 2 during the first week of randomized treatment. A total of 7 dropped out before completing first week post randomization: 3 due to adverse effects (2 from immediate-release methylphenidate group and 1 from control group), 3 who indicated their preference for not being at risk for placebo treatment and 1 due to noncompliance It appears that after 1 week completion of randomised treatment, no further participants dropped out
Tenenbaum 2002	27% 9 / 33	No ITT analysis. 9 participants discontinued due to noncompliance with medication or appointments. It is not clear from which group they were dropped and why they were not compliant. Baseline scores of completers versus noncompleters were compared with no important difference. Exclusion from analysis: no data given
Bouffard 2003	21% 8 / 38	No ITT analysis was carried. Reasons: 1 - due to adverse effects, 4 - not blind to methylphenidate, 1 - "too much going on", 2 - unknown
Kooij 2004	No dropouts reported.	
Spencer 2005	24% 36 / 146	No ITT analysis. Dropouts: 10 participants prior to completion of 2 weeks of treatment, 26 prior to trial completion. Dropout rate did not differ between medication and placebo (25% (26 / 104) versus 24% (10 / 42)). Of reasons for dropout, only "no effect" was important (placebo > immediate-release methylphenidate)

Table 3. Dropouts (*Continued*)

		Dropouts excluded from analysis.
Wender 2011	9% 11 / 116	No ITT analysis, no reason for dropout reported or distribution between groups. No information is given as to inclusion in analysis

ITT - intention-to-treat.

Table 4. Hyperactivity

Study	Results	Comments
Wood 1976	(N = 11, SMD -1.38, 95% CI -2.74 to -0.01)	Presented as self-rating on an "energetic - tired" scale.
Wender 1985	(N = 37, SMD -0.92, 95% CI -1.41 to -0.43)	Presented as Physician's target symptom ratings on a 7-point Global Assessment Scale
Spencer 1995	(N = 23, SMD -1.09, 95% CI -1.56 to -0.62)	Hyperactivity subscale of the ADHD Rating Scale.
Tenenbaum 2002	(N = 24, SMD 0.39, 95% CI 0.02 to 0.76)	Measured on the overactivity / hyperactivity subscale of the Copeland Symptom Checklist for Adult ADD
Kooij 2004	(N = 45, SMD -0.21, 95% CI -0.48 to 0.06)	Measure on the Dutch self report version of the DSM-IV ADHD rating scale
Wender 2011	(N = 105, SMD -0.89, 95% CI -1.25 to -0.52]	Hyperactivity score on the WRAADDS

ADD - attention deficit disorder.
ADHD - attention deficit hyperactivity disorder.
CI - confidence interval.
DSM IV - Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.
SMD - standardized mean difference.
WRAADDS - Wender-Reimherr Adult Attention Deficit Disorder Scale.

Table 5. Impulsivity

Study	Results	Comments
Wood 1976	N = 11, SMD -1.41, 95% CI -2.53 to -0.29	Measured on self-report, 'hot tempered - cool tempered' scale
Spencer 1995	N = 23, SMD -1.42, 95% CI -2.24 to -0.60	Data from the impulsivity subscale of the ADHD Rating Scale.
Tenenbaum 2002	N = 23, SMD 0.05, 95% CI -0.53 to 0.63	Data from the Barrat Impulsiveness Scale.
Kooij 2004	N = 45, SMD -0.23, 95% CI -0.40 to -0.06	Data from the impulsivity subscale of the DSM-IV ADHD Rating Scale

Table 5. Impulsivity (*Continued*)

Wender 2011	N = 105, SMD -0.78, 95% CI -1.09 to -0.47	Data from the impulsivity score on the WRAADDS.

ADHD - attention deficit hyperactivity disorder.
CI - confidence interval.
DSM IV - Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.
SMD - standardized mean difference.
WRAADDS - Wender- Reimherr Adult Attention Deficit Disorder Scale.

Table 6. Inattentiveness

Study	Result	Comments
Wood 1976	(N = 11, SMD -1.46, 95% CI -2.70 to -0.22)	Data used was the outcome on a self-rated 'concentrating - mind wandering' scale
Wender 1985	(N = 37, SMD -1.10, 95% CI -1.73 to -0.46)	Data from the 'short attention span' score on the Physician Target Symptom Scale
Spencer 1995	(N = 23, SMD -0.81, 95% CI -1.48 to -0.15)	Data from the the 'inattentiveness' subscale of the ADHD Rating Scale
Tenenbaum 2002	(N = 24, SMD -0.02, 95% CI -0.59 to 0.54)	Data based on the Brown Attention Deficit Disorder Scales.
Kooij 2004	(N = 45, SMD -0.20, 95% CI -0.43 to 0.03)	Data based on the 'inattention' subscale of the DSM IV ADHD Rating Scale
Spencer 2005	(N = 104, SMD -0.57, 95% CI -0.93 to -0.21)	Data based on the Adult ADHD Investigator' System Report Scale and was extracted from a graph presentation. We were unable to receive the exact numerical data which was not presented in the publication itself. Since this was a parallel study, N = treatment arm only
Wender 2011	(N = 105, SMD -1.07, 95% CI -1.45 to -0.69)	Data based on the attention difficulties score on the WRAADDS

ADHD - attention deficit hyperactivity disorder.
DSM IV - Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.
WRAADDS - Wender-Reimherr Adult Attention Deficit Disorder Scale.

Table 7. Low dose

Category	Study	Result
Impulsivity	Wood 1976	N = 11, SMD -1.41, 95% CI -2.53 to -0.29
	Tenenbaum 2002	N = 23, SMD 0.05, 95% CI -0.53 to 0.63

Table 7. Low dose (*Continued*)

	Wender 2011	N = 105, SMD -0.78, 95% CI -1.09 to -0.47
Hyperactivity	Wood 1976	N = 11, SMD -1.38, 95% CI -2.74 to -0.01
	Wender 1985	N = 37, SMD -0.92, 95% CI -1.41 to -0.43
	Tenenbaum 2002	N = 24, SMD 0.39, 95% CI 0.02 to 0.76
	Wender 2011	N = 105, SMD -0.89, 95% CI -1.25 to -0.52
Inattentiveness	Wood 1976	N = 11, SMD -1.46, 95% CI -2.70 to -0.22
	Wender 1985	N = 37, SMD -1.10, 95% CI -1.73 to -0.46
	Tenenbaum 2002	N = 24, SMD -0.02, 95% CI -0.59 to 0.54
	Wender 2011	N = 105, SMD -1.07, 95% CI -1.45 to -0.69

CI - confidence interval.
SMD - standardized mean difference.

Table 8. Original Data

Original Data Table								
		Placebo			**Methylphenidate**			
		N	**SD**	**Mean**	**N**	**SD**	**Mean**	**Comments**
Hyperactivity	Wood 1976	11	1.16	3.25	11	1.15	1.66	
	Wender 1985	37	0.95	3.29	37	1.11	2.33	
	Spencer 1995	23	-	1.88 (0.2)	23	-	0.84 (0.2)	Baseline 2.04 (0.2 SEM)
	Tenenbaum 2002	24	19.3	36.8	24	21.8	44.9	Baseline 53.3 (20.8 SD)
	Kooij 2004	-	-	-	-	-	-	SMD -0.13857, SE 0.09122449 SMD and P value from paired t-test
	Wender 2011	105	1.3	2.6	105	1.4	1.4	Baseline 3 (0.9 SD)
Impulsivity	Wood 1976	11	1.63	3.55	11	0.99	1.65	

Table 8. Original Data (*Continued*)

	Spencer 1995	23	-	1.99 (0.2)	23	-	0.91(0.1)	Baseline 2.55 (0.1 SEM)
	Tenenbaum 2002	23	1.1	0.54	23	1	0.49	
	Kooij 2004	-	-	-	-	-	-	SMD -0.23139 SE 0.08607143 SMD and P value from paired t-test
	Wender 2011	105	1.1	1.8	105	1.2	0.9	Baseline 2.2 (0.9 SD)
Inattentiveness	Wood 1976	11	1.38	3.28	11	0.54	1.75	
	Wender 1985	37	0.95	3.35	37	1.02	2.27	
	Spencer 1995	23	-	2.28 (0.1)	23	-	1.89 (0.1)	Baseline 2.51 (0.1 SEM)
	Tenenbaum 2002	24	1.5	1.11	24	2	1.15	
	Kooij 2004	-	-	-	-	-	-	SMD -0.20385 SE 0.11716837 SMD and P value from paired t-test
	Spencer 2005	42	4	17	104	2	8	Estimated from graph Placebo 21 (3 SEM) MPH 20 (3 SEM)
	Wender 2011	105	1.4	2.9	105	1.4	1.4	Baseline 3.1(0.9 SD)
Overall Change - continuous data	Mattes 1984	26	1.24	4.58	26	1.39	4.42	
	Wender 1985	37	6.16	0.16	37	1.64	1.40	
	Tenenbaum 2002	24	3.7	2.54	24	4.1	2.98	
	Bouffard 2003	30	0.6	1.4	30	0.6	1.0	Baseline 1.9 (0.4 SD)
	Kooij 2004	45	1.7	4.4	45	1.5	5.4	

Table 8. Original Data (*Continued*)

	Spencer 2005	42	11.2	28	104	10.3	13.1	
	Wender 2011	105	7	16	105	7.9	8	Baseline 17.6 (5.2 SD)
Overall Change - dichotomous data	Spencer 1995	23	-	4% (1 / 23)	23	-	78% (18 / 23)	Responders
	Kuperman 2001	11	-	27%	8	-	50%	Responders

N - number.
SD - standard deviation.
SDM - standardized mean difference.
SE - standard error.
SEM - structural equation modelling.

Table 9. High dose

Category	Study	Results	Comments
Impulsivity	Spencer 1995	N = 23, SMD -1.42, 95% CI -2.24 to -0.60	
	Kooij 2004	N = 45, SMD -0.23, 95% CI -0.40 to -0.06	
Hyperactivity	Spencer 1995	N = 23, SMD -1.09, 95% CI -1.56 to -0.62	
	Kooij 2004	N = 45, SMD -0.21, 95% CI - 0.48 to 0.06	
Inattentiveness	Spencer 1995	N = 23, SMD -0.81, 95% CI -1.48 to -0.15	
	Kooij 2004	N = 45, SMD -0.20, 95% CI -0.43 to 0.03	
	Spencer 2005	N = 104, SMD -0.57, 95% CI -0.93 to -0.21	Since this was a parallel study, N = treatment arm only.

CI - confidence interval.
SMD - stnandardized mean difference.

Table 10. Overall change (continuous data)

Study	Result	Comments
Mattes 1984	N = 26, SMD -0.12, 95% CI -0.67 to 0.42	Assessed change using Global Improvement Rating.
Wender 1985	N = 37, SMD 0.28, 95% CI -0.83 to 1.38	Assessed change using the Physicians' Global Rating Scale, similar to the CGI Scale
Tenenbaum 2002	N = 24, SMD -0.11, 95% CI -0.68 to 0.45	Assessed overall change with a number of different scales (Barkely's, Copeland, and ADSA scales). We chose to incorporate data from the Copeland Scale because this scale contains subscales for the 3 domains of inattention, hyperactivity, and impulsivity
Bouffard 2003	N = 30, SMD -0.67, 95% CI -1.23 to-0.11	Assessed change by change on the Conners' Rating Scale. Data for both a higher dose (15 mg 3 times daily) and a lower dose (10 mg 3 times daily) were provided. We opted to include the data for the higher dose used
Kooij 2004	N = 45, SMD -0.62, 95% CI -1.08 to -0.17)	Assessed change by change on the CGI Scale.
Spencer 2005	N = 104, SMD -1.40, 95% CI -1.80 to -1.01	Assessed change by change on the CGI scale. Since this was a parallel study, N = treatment arm only
Wender 2011	N = 105, SMD -1.07, 95% CI -1.41 to -0.73	Assessed change using the total score of the WRAADDS.

ADSA - Attention Deficit Scales for Adults.
CGI - clinical global impression.
CI - confidence interval.
SMD - standardized mean difference.
WRAADDS - Wender-Reimherr Adult Attention Deficit Disorder Scale.

Table 11. Overall change (dichotomous data)

Study	Result	Comments
Spencer 1995	N = 23, SMD -2.41, 95% CI -3.64 to -1.18	Defined responders as participants who had a CGI score of 2 or less and a reduction of at least 30% in individual rating scales scores
Kuperman 2001	N = 8, SMD -0.54, 95% CI -1.60 to 0.52	Reported on responders versus nonresponders (responders were those who improved on 1 or more CGI score, as rated by a clinician). Since this was a parallel study, N = treatment arm only

CGI - clinical global impression.

Table 12. Adverse effects

Study	Type of adverse effect	Rates and changes
Wood 1976	No reported adverse effects	
Mattes 1984	Appetite and weight	Significantly more anorexia reported in immediate-release methylphenidate group ($P < 0.05$)
	Other	Significantly more headaches reported in immediate-release methylphenidate group ($P < 0.05$)
Gualtieri 1985	Cardiovascular	Adverse effects were not reported specifically, but pulse and blood pressure were measured and small and nonsignificant increases in pulse and systolic and diastolic blood pressure were reported
Wender 1985	General	8 out of 37 (21%) reported adverse effects only while taking immediate-release methylphenidate versus 10% while on placebo. Among the adverse effects reported were insomnia, mild anxiety, jaw tension, tooth grinding, overstimulation, irritability, and nose tingling. The specific rates or significance for the various adverse effects were not reported
Spencer 1995	General	Rates of subjective adverse effects did not differ with placebo and immediate-release methylphenidate, but were more pronounced with immediate-release methylphenidate
	Appetite and weight	Loss of appetite most common adverse effect (26%). Significant decrease in weight (73.2 kg vs 74.3 kg)
	Cardiovascular	Significant increase in heart rate with immediate-release methylphenidate (80 vs 76). Nonsignificant rise in systolic (123 vs 117) and diastolic blood pressure (77 vs 75)
	Other	Insomnia (22%), anxiety (22%).
Kuperman 2001	General	Similar numbers of adverse effects reported for placebo and immediate-release methylphenidate
	Appetite and weight	3 of 12 participants in the immediate-release methylphenidate group reported decreased appetite
	Other	Insomnia, tremor, sweating, and jitteriness reported each in 2 out of 12 immediate-release methylphenidate participants
Tenenbaum 2002	No reported adverse effects	
Bouffard 2003	Appetite and weight	41% of immediate-release methylphenidate group reported appetite suppression versus 23% at baseline and 19% for placebo. No significant weight loss reported

Table 12. Adverse effects (*Continued*)

	Cardiovascular	1) Blood pressure increase with immediate-release methylphenidate - mean 124 mmHg at baseline and 123 mmHg for placebo versus 128 mmHg for immediate release methylphenidate P < 0.01. 2) Nonsignificant heart rate increase with immediate-release methylphenidate
	Other	Insomnia improved under immediate-release methylphenidate (41% at baseline vs 25% on placebo and 26% on immediate-release methylphenidate)
Kooij 2004	Appetite and weight	Loss of appetite, only adverse effect which occurred significantly more often with immediate-release methylphenidate (22% vs 4% P value = 0.039). Mean weight loss of 1.7 kg (P < 0.001) reported
	Cardiovascular	Nonsignificant rise in complaints of tachycardia (9% vs 2% P value = 0.25), and a mean of 4.8 beats / minute elevation with immediate-release methylphenidate (P value = 0.002)
	Other	Nonsignificant rise in sleeping problems (33% vs 22% P value = 0.27), headache (16% vs 4% P value = 0.18), dizziness (16% vs 7% P value = 0.34), abdominal complaints (13% vs 4% P value = 0.22), dry mouth (24% vs 7% P value = 0.06), and tics (7% vs 2% P value = 0.5)
Spencer 2005	General	Appetite suppression, dry mouth, pulse increase, and mild moodiness were the only adverse effects with statistical significance
	Appetite and weight	Appetite decrease with immediate-release methylphenidate versus placebo (27% vs 7% P value = 0.01). Weight decrease of 2.4 kg on average with immediate-release methylphenidate. Dry mouth and moodiness both increased
	Cardiovascular	Significant increase in pulse (83% vs 76%) P < 0.001). No significant increase in mean blood pressure
	Other	Dry mouth (35% vs 0% P value = 0.001) and moodiness (30% vs 5% P value = 0.001) were notable in immediate-release methylphenidate group versus placebo
Wender 2011	General	All adverse events were minor. 15% of placebo patients experienced 20 side effects with headache most common. In the methylphenidate arm 19% of patients experienced 59 side effects with headache, appetite loss, nervousness, insomnia and dry mouth the most common ones. No patient withdrew because of side effects
	Appetite and weight	Appetitle loss was noted by 8 / 105 participants in the methylphenidate group versus 1 / 105 in the placebo group. No weight loss was noted
	Cardiovascular	There was no significant treatment effect on pulse or blood pressure

APPENDICES

Appendix 1. Database search strategies

Cochrane Central Database of Controlled Trials (CENTRAL)
CENTRAL 2013(10) searched November 27, 2013.
CENTRAL previously searched October 16, 2012, June 21, 2011, and July 2009.
1MeSH descriptor: [Methylphenidate] explode all trees
#2methylphenidate
#3ritalin
#4#1 or #2 or #3
#5MeSH descriptor: [Attention Deficit Disorder with Hyperactivity] this term only
#6adhd
#7addh
#8(hyperactiv*)
#9(hyperkin*)
#10(attention next deficit*)
#11(brain next dysfunction)
#12(#5 or #6 or #7 or #8 or #9 or #10 or #11)
#13 #4 and #12
Ovid MEDLINE(R)
Ovid MEDLINE 1946 to November Week 2 2013, searched November 27, 2013.
Ovid MEDLINE previously searched October 16, 2012, June 21, 2011, and July 2009.
1 Attention Deficit Disorder with Hyperactivity/
2 adhd.tw.
3 addh.tw.
4 hyperactiv$.tw.
5 hyperkin$.tw.
6 attention deficit$.tw.
7 brain dysfunction.tw.
8 or/1-7
9 Methylphenidate/
10 methylphenidate.tw.
11 ritalin.tw.
12 or/9-11
13 randomized controlled trial.pt.
14 controlled clinical trial.pt.
15 randomi#ed.ab.
16 placebo$.ab.
17 drug therapy.fs.
18 randomly.ab.
19 trial.ab.
20 groups.ab.
21 or/13-20
22 exp animals/ not humans.sh.
23 21 not 22
24 8 and 12 and 23
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
November 26, 2013, searched November 27, 2013.
1 adhd.tw.
2 addh.tw.
3 hyperactiv$.tw.
4 hyperkin$.tw.

5 attention deficit$.tw.
6 brain dysfunction.tw.
7 or/1-6
8 methylphenidate.tw.
9 ritalin.tw.
10 8 or 9
11 7 and 10
12 placebo$.ab.
13 trial.ab.
14 groups.ab.
15 random$.tw.
16 12 or 13 or 14 or 15
17 11 and 16

EMBASE (Ovid)

EMBASE 1980 to 2013 Week 47, searched November 27, 2013.
EMBASE previously searched 16 October 2012, June 21, 2011, and July 2009.
1 Attention Deficit Disorder/
2 adhd.tw.
3 addh.tw.
4 hyperactiv$.tw.
5 hyperkin$.tw.
6 attention deficit$.tw.
7 brain dysfunction.tw.
8 or/1-7
9 Methylphenidate/
10 methylphenidate.tw.
11 ritalin.tw.
12 or/9-11
13 8 and 12
14 random$.tw.
15 factorial$.tw.
16 crossover$.tw.
17 cross-over$.tw.
18 placebo$.tw.
19 (doubl$ adj blind$).tw.
20 (singl$ adj blind$).tw.
21 assign$.tw.
22 allocat$.tw.
23 volunteer$.tw.
24 Crossover Procedure/
25 double-blind procedure.tw.
26 Randomized Controlled Trial/
27 Single Blind Procedure/
28 or/14-27
29 13 and 28**PsycINFO (Ovid)**

PsycINFO 1806 to November Week 3 2013, searched November 27, 2013.
PsycINFO previously searched via Ovid October 17, 2012, and July 2009.
PsycINFO also searched via EBSCOhost in June 2011.
1.attention deficit disorder with hyperactivity/
2 (adhd or addh or hyperactiv$ or hyperkin$ or attention deficit$).tw.
3 brain dysfunction.tw.
4 or/1-3
5 methylphenidate/

6 ritalin.mp.
7 (methylphenidate or ritalin).mp.
8 or/5-7
9 4 and 8
10 clinical trials/
11 (trial$ or random$ or crossover$ or blind$ or RCT).tw.
12 10 or 11
13 9 and 12

PsycINFO (EBSCOhost)

PsycINFO 1887 to current, searched June 21, 2011.
PsycINFO also searched via Ovid in November 2013, October 2012, and July 2009.
S13 S9 and S12
S12 S10 or S11
S11 trial* or random* or crossover or blind*
S10 DE "Clinical Trials"
S9 S4 and S8
S8 S5 or S6 or S7
S7 ritalin
S6 methylphenidate
S5 DE "Methylphenidate"
S4 S1 or S2 or S3
S3 brain dysfunction
S2 adhd or addh or hyperactiv* or hyperkin* or attention deficit*
S1 DE "Attention Deficit Disorder with Hyperactivity"

Biosis Previews (Web of Knowledge)

Biosis January 1990 to December 2013, searched on December 12, 2013.
Biosis previously searched October 2012, June 2011, and July 2009.
10 #9 AND #3
9 #8 OR #7 OR #6 OR #5 OR #4
8 TS=(clin* SAME trial*)
7 TS=((singl* or doubl* or tripl* or trebl*) SAME (blind* or mask*))
6 TS=(randomi*)
5 TS=(random* SAME (allocat* or assign*))
4 TS=(crossover)
#3 #2 AND #1
2 TS=(methylphenidate) or TS=(ritalin)
1 TS=(adhd) or TS=(addh) or TS=(hyperactiv*) or TS=(hyperkin*) or TS=(attention deficit*) or TS=(brain dysfunction)

Database of Reviews of Effects (DARE)

DARE 2013(4), searched November 27, 2013.
DARE previously searched October 18, 2012, June 21, 2011, and July 2009.
#1MeSH descriptor: [Methylphenidate] explode all trees
#2methylphenidate:ti,ab
#3ritalin:ti,ab
#4#1 or #2 or #3
#5MeSH descriptor: [Attention Deficit Disorder with Hyperactivity] this term only
#6adhd:ti,ab
#7addh:ti,ab
#8(hyperactiv*):ti,ab
#9(hyperkin*):ti,ab
#10(attention next deficit*):ti,ab
#11(brain next dysfunction):ti,ab
#12(#5 or #6 or #7 or #8 or #9 or #10 or #11)

#13(#4 and #12)
Cochrane Database of Systematic Reviews (CDSR)
CDSR 2013 (11), searched November 27, 2013.
#1MeSH descriptor: [Methylphenidate] explode all trees
#2methylphenidate:ti,ab
#3ritalin:ti,ab
#4#1 or #2 or #3
#5MeSH descriptor: [Attention Deficit Disorder with Hyperactivity] this term only
#6adhd:ti,ab
#7addh:ti,ab
#8(hyperactiv*):ti,ab
#9(hyperkin*):ti,ab
#10(attention next deficit*):ti,ab
#11(brain next dysfunction):ti,ab
#12(#5 or #6 or #7 or #8 or #9 or #10 or #11)
#13(#4 and #12) in Cochrane Reviews (Reviews only) (Word variations have been searched)
ICTRP
ICTRP searched November 28, 2013, October 18, 2012, June 25, 2011.
adhd AND METHYLPHENIDATE
ClinicalTrials.gov
ClinicalTrials.gov searched November 27, 2013, October 18, 2012, June 25, 2011.
CONDITION: ADHD OR hyperactive
INTERVENTION: methylphenidate
Limited to ADULTS (18-65 yrs)

Appendix 2. Numbers of records found by the searches

Records found in databases in the first search conducted in July 2009:
CENTRAL 2009 (Issue 3)-843 records
MEDLINE 1950 to July 17, 2009-2275 records
EMBASE 1980 to 2009 Week 29-786 records
PsycINFO 1806 to July Week 2 2009-1455 records
BIOSIS 1985 to July 2009-356 records
A total of 5715 records
Records found in databases in the second search conducted in June 2011:
CENTRAL July 2009 to June 2011-67 records
MEDLINE July 2009 to June 2011-272 records
EMBASE July 2009 to June 2011-183 records
PsycINFO July 1, 2009 to June 2011-249 records
BIOSIS July 2009 to June 2011-90 records
Clinicaltrials.gov-all years, searched on June 25, 2011-72 records
ICTRP-all years, searched on August 22, 2011-168 records
DARE-all years, searched on June 21, 2011-7 records
A total of 1108 records
Records found in databases in the third search, conducted in October 2012:
CENTRAL June 2011 to October 2012-31 records
MEDLINE June 2011 to October 2012-262 records
EMBASE June 2011 to October 2012-168 records
PsycINFO June 2011 to October 2012-76 records
BIOSIS June 2011 to December 2012-67 records
ClinicalTrials.gov August 22, 2011, to October 18, 2012-6 records
ICTRP August 22, 2011, to October 18, 2012-6 records

DARE June 2011 to October 2012-3 records
A total of 619 records
Records found in databases in the fourth search conducted in November 2013:
Cochrane Library (CENTRAL) October 2012 to November 2013-19 records
Ovid MEDLINE October 2012 to November 2013-168 records
Ovid MEDLINE In-Process & Other Indexed Citations-97 records
EMBASE October 2012 to November 2013-181 records
PsycINFO October 2012 to November 2013-65 records
BIOSIS December 2012 to December 2013-40 records
Clinicaltrials.gov October 2012 to November 2013-8 records
ICTRP October 2012 to November 2013-24 records
DARE October 2012 to November 2013-3 records
CDSR October 2012 to November 2013-1 record
A total of 606 records

FEEDBACK

Methodological concerns, 29 October 2014

Summary

After reading carefully your systematic review entitled "*Methylphenidate for attention-deficit/hyperactivity disorder in adults*", we would like to share with you some comments and concerns. All of them are aimed at strengthening the quality of the review.
The authors state that "overall, the body of evidence about use of methylphenidate in adults with ADHD is of high quality. It shows that methylphenidate improves ADHD symptoms in adults and suggests that side effects are not serious". However, there seems to be some relevant aspects contradicting these previous statements that would deserve a more in-depth discussion.
1. According to GRADE, a "high quality" grade of evidence can be considered when "further research is very unlikely to change our confidence in the estimate of effect". But this review includes 11 studies with only 474 participants, so new information from larger additional clinical trials should be welcomed and clearly could still change the estimate of effect.
2. In the Abstract, it is claimed that all included studies "in general, did not contain factors that significantly decreased the quality of the body of evidence". However we think there are enough reasons to conclude the opposite. GRADE establishes five factors to be considered: a) Limitations in the design and implementation of available studies; b) Indirectness of evidence; c) Unexplained heterogeneity or inconsistency of results; d) Imprecision of results; and e) High probability of publication bias. What can be said about these five factors?
a. *Design*: Most of studies included (9 out 11) are extremely small (< 50 participants). Participants are included based on different DSM criteria with significant differences. For example, DSM III (1980) makes emphasis on lack of attention that is accompanied or not by hyperactivity; DSM III-R (1987) encompass two subtypes in one; and DSM IV (1994) now divides the only category into three subtypes. ADHD diagnosis has little to do with real practice in 80's, 90's or 00's. Furthermore, there is no information on allocation concealment and random sequence generation (only partial data from Kooij 2004). Finally, it reads that authors "opted to synthesize all clinically homogenous scales" but there is no information about what criteria were pre-defined in order to judge scales as "clinically homogenous". Also, inclusion of non validated scales can easily lead to misleading results.
b. *Indirectness*: No specific comment on this factor.
c. *Unexplained heterogeneity*: This systematic review shows very large, unexplained statistical heterogeneity ($I^2 > 75\%$). It is admitted that heterogeneity "could not be explained by differences in dosage" and "the number of studies per outcome was not adequate to permit proper exploration of possible sources of heterogeneity". The authors consider that the "decision to refrain from synthesizing data - in light of the high level of heterogeneity - may have led to "vote counting," which is advised against in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Because a small number of studies, most of which included a small number of participants, were identified, we chose to synthesize results using a random-effects meta-analysis model." However, in our opinion, this major issue should have led to avoid performing a quantitative meta-analysis. While it is true that "vote counting" is not recommended by the *Cochrane Handbook*, synthesizing data is not the only alternative, and let alone a mandatory approach. In fact, the *Cochrane*

Handbook states that "if overall results are not calculated in the review, a qualitative assessment or a description of the range and pattern of the results can be given". That would have probably been the best way to proceed. On the other hand, choosing a random-effects instead of a fixed-effect model do not solve the problem of very large heterogeneity.

d. *Imprecision of results*: Concerning the confidence intervals of the main variables, they are wide enough to be compatible with large (> 0.70), moderate (0.40 to 0.70) or even small (< 0.40) effect sizes (see *Cochrane Handbook* 5.1.0, section 12.6.2). According to this, when authors claim that "the body of evidence includes some factors that may increase the quality level, such as a large magnitude of effect", this is not an acceptable statement. A 0.6 size effect in SMD is considered as a moderate, but not a large effect size.

e. *Publication bias*: Because of scarcity of studies, little can be said on external publication bias. However, it must be noted that the largest parallel study included (Spencer 2005) was described as high reporting risk of bias and this kind of bias can be considered as a subtype of publication bias within a study.

Taking all of this into account, we conclude that 1) we find enough reasons to downgrade the quality of the evidence in main outcomes and 2) performing a quantitative meta-analysis was not probably the best choice in order to show the results.

In any case, it is difficult to understand why two outcomes as hyperactivity and inattentiveness, whose data come from the same six studies (Kooij 2004, Spencer 1995, Tenenbaum 2002, Wender 1985, Wender 2011 and Wood 1976), receive a different opinion on quality of the evidence, namely "high" for hyperactivity and "moderate" for inattentiveness. While it is true that the Spencer 2005 study provides data on inattentiveness but not on hyperactivity outcomes, a better rate for inattentiveness could not be based on this fact only. It could be explained because the study mentioned above did not score well in the risk of bias assessment (three positive, two unclear and one negative criteria), and thereby no relevant changes should be expected out of it.

3. Despite most trials (9 out of 11) were cross-over studies, no discussion about potential carry-over effect or any other specific bias linked to this particular design is available in the review (*Cochrane Handbook* 5.1.0, 16.4.3 section). Similarly, the *Handbook* asks authors (16.4.7 section) to "explicitly state how they have dealt with data from cross-over trials and should conduct sensitivity analyses to investigate the robustness of their conclusions". Unfortunately, no sensitivity analysis was performed to explore this matter. Besides, looking at the relevant differences between protocol and review, a sensitivity analysis could have also been useful to check on what extent this decision has altered the outcome results.

Authors' conclusions also state that "Data from randomized controlled trials suggest that immediate-release methylphenidate is efficacious for treating adults with ADHD with symptoms of hyperactivity, impulsivity, and inattentiveness, and for improving their overall clinical condition". While it is admitted that "these results may be applicable only to studies of a similarly short duration" and "would have been valuable (…) an outcome measure of overall functioning or quality of life, especially after a long course of treatment", evidence is surprisingly considered as "highly relevant".

How should we interpret these results that are focused only on symptoms, come from short-term studies (shorter than six weeks) and use standardized mean differences (SMD) as the effect measure? As Egger et al state (Egger M, Smith GD, Altman D: *Systematic Reviews in Health Care: Meta-Analysis in Context* [2008] wiley.com), the overall treatment effect [in terms of SMD] can be difficult to interpret as it is reported in units of standard deviation rather than in units of any of the measurement scales used in review. Thus, what does a 0.6 size effect in SMD really mean? In our view, when methylphenidate is said to be "efficacious", too narrow a definition of this concept has been used. If we want to talk about efficacy, we probably need other kind of data better related to real patients' needs (long-term effects, outcomes on relevant variables, clear interpretation of results, etc.).

4. The review also concludes that "none of these results [adverse effects] were judged to present cause for concern". However, it has already been noted that all studies included were short-term. In real practice methylphenidate is used in the long term, and a continuous rise of blood pressure or heart rate in adults should be a matter of concern.

5. Lastly, we think it is important to make a comment on the way authors deal with conflicts of interest in the review. In spite of the fact that many studies included or referenced were carried out by authors with evident links to ADHD-related drug companies, no discussion on this matter is provided by review authors. We honestly consider this issue would deserve more attention, even if Cochrane and PRISMA do not require explicitly that trial funding sources be reported. On the other hand, regarding review authors, it can be read in the *Cochrane Handbook* (Section 2.6) that "financial conflicts of interest cause the most concern, can and should be avoided, but must be disclosed if there are any". In this case, a majority of review authors (two out of three) declare some financial conflict of interest. We agree with the *Cochrane Handbook* (Section 2.6) when it states that "conflicts of interest can influence judgements in subtle ways" and, in our opinion, considering all the limitations discussed above, the Cochrane Developmental, Psychosocial and Learning Problems Group should have prioritized a free-conflict of interest review for this relevant topic.

Thank you for your interest, and we hope this feedback is useful to our shared aim of improving the standard of Cochrane reviews.

Contributor agrees with statement: *We certify that we have no affiliations with, or involvement in, any organization or entity with a financial interest in the subject matter of our feedback.*

Reply

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Adverse effects, 17 November 2014

Summary

The last sentence of the abstract concludes that "adverse effects of immediate-release methylphenidate are not .... (clinically) serious ...although this conclusion MAY BE limited, certainly in the case of weight loss, by the short duration of published studies" (capitals added). ... Surely, it IS limited.
Further, the abstract does not mention the duration of the studies: that deserves a few words - please add them.... please [also] explain what you mean by "clinically serious" as compared with "serious" in the patient's view.

Contributor agrees with statement:*I certify that I have no affiliations with, or involvement in, any organization or entity with a financial interest in the subject matter of my feedback.*

Reply

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Methodological concerns, 17 April 2015

Summary

I am wondering why the authors of this review on immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults judged the overall quality of evidence as "high".
Most of the studies did not report methods for blinding and concealment of allocation, besides several other methodological limitations. In general, the studies included in this review could be judged of poor methodological quality and the risk of bias graph clearly demonstrated this: most information to judge risk of bias was unclear in almost all trials - especially randomization sequence and allocation concealment. A rating of "high" quality evidence can be achieved only when most evidence included in a systematic review comes from studies that most probably or certainly used concealed allocation, all blinded at least some key groups and follow-up of randomized patients was almost complete (*Cochrane Handbook of Interventions*, Chapter 12). Considering GRADE recommendations, I do not see how the evidence gathered in this systematic review could be of high quality.

In addition, the majority of the trials included in the review applied cross-over design. Cross-over designs are prone to additional types of bias in comparison with trials applying parallel design (detailed in *Cochrane Handbook* Chapter 16). The main concerns over risk of bias in cross-over trials did not appear to be taken into account in the review.
Contributor agrees with statement: *I certify that I have no affiliations with, or involvement in, any organization or entity with a financial interest in the subject matter of my feedback.*

Reply

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Methodological concerns, 10 May 2015

Summary

We have carefully read your review Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults published in the*Cochrane Library* in issue 9, 2014. You conclude that "immediate-release methylphenidate is efficacious for treating adults with ADHD with symptoms of hyperactivity, impulsivity, and inattentiveness, and for improving their overall clinical condition. Trial data suggest that adverse effects from immediate-release methylphenidate for adults with ADHD are not of serious clinical significance, although this conclusion may be limited, certainly in the case of weight loss, by the short duration of published studies". Furthermore, you state that "overall, the body of evidence about use of methylphenidate in adults with ADHD is of high quality. It shows that methylphenidate improves ADHD symptoms in adults and suggests that side effects are not serious".

We do not agree with the assessment of the quality of included studies and we do not agree with your conclusions. We judge all the trials in this particular review to be at high risk of bias; the meta-analyses show high inconsistency between studies, and the estimates are highly imprecise. Your review showed the SMD for the outcome of hyperactivity was -0.60 (95% CI -1.11 to -0.09, 6 studies, number of participants (n) = 245, high-quality evidence). All the studies in this meta-analysis were high risk of bias studies (most of the studies had three or more unclear risk of bias domains), the heterogeneity was I^2 = 80% and the 95% confidence interval was wide, from -1.11 to -0.09. In our opinion this outcome should have been downgraded to very low quality in the GRADE assessment.
The SMD for impulsivity was -0.62 (95% CI -1.08 to -0.17, 5 studies, (n = 207), high-quality evidence). All the studies in this meta-analysis were high risk of bias studies (most of the studies had three or more unclear risk of bias domains), the heterogeneity was I^2 = 81% and the 95% confidence interval was wide. In our opinion this outcome should also have been downgraded to very low quality in the GRADE.

You state that there are some factors also that may increase the quality level such as high magnitude of effect. We are not sure which 'high magnitude effect' you are referring to?

We therefore strongly believe that your conclusion is incorrect. Based on our assessments of your evidence, our conclusion is that it is not possible at present to either recommend or refute methylphenidate for adults with ADHD.
Contributor agrees with statement: *I certify that I have no affiliations with, or involvement in, any organization or entity with a financial interest in the subject matter of my feedback.*

Reply

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Methodological concerns, 30 November 2015

Summary

The conclusions in the systematic Cochrane review "Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults" by Epstein et al. provide a misleading sense of certainty of benefits and harms and the review must be substantially revisited, or withdrawn.

The systematic review by Epstein et al. has several major flaws. The review did not take into account the extensive criticism of the included trials that has already been published (1). Indeed, its conclusions that immediate-release methylphenidate is efficacious, that harms are "not of serious clinical significance" and that the evidence is of high quality for most outcomes are not supported by the data.

First, Epstein et al. assessed the evidence as "high quality" for most outcomes using the GRADE tool, despite the majority of domains in the Cochrane Risk of Bias tool for the included trials being labelled as "unclear". This should lead to downgrading the confidence. Heterogeneity for the ADHD outcomes hyperactivity, inattention and impulsivity was between 76% and 88%. This should also lead to downgrading, as the heterogeneity was not explained. These two items alone would lead to the confidence in the evidence being classified as "low" or "very low". Epstein et al. wrote that the body of evidence included "factors that may increase the quality level, such as a large magnitude of effect" (p 21). Not only were the estimated effects moderate (SMDs between -0.6 to -0.72), it is also a conceptual misunderstanding of the GRADE tool where the possibility to upgrade is reserved for observational studies, which start as low quality evidence. Randomised clinical trials start as high quality evidence and can generally be downgraded only, whereas observational studies may be upgraded if the effect size is very large. While the GRADE Handbook notes that upgrading results from randomised trials is "theoretically possible", they "have yet to find a compelling example of such an instance", and it would require that there are no serious limitations in any of the five domains for downgrading (GRADE Handbook, Chapter 5.3) (2). Epstein et al. abstained from exploring reasons for the heterogeneity, except low dosage versus high dosage, arguing that they had too few studies for meta-regression. Simple sensitivity analyses would be adequate in most cases, and exploring reasons for substantial heterogeneity should never be neglected.

Second, Epstein et al. included 11 trials in the systematic review, 9 of which were cross-over designs. The cross-over design is highly questionable in this context due to the risk of carry-over effects, and due to ADHD not being a "stable" condition where "long-term follow-up is not required", which are prerequisites for the cross-over design to be suitable (*Cochrane Handbook*, Chapter 16.4.3) (3). Methylphenidate is a central-stimulating drug related to amphetamine and abrupt withdrawal can lead to rebound symptoms. The authors of a parallel group trial acknowledged the risk of carry-over effects (4) referring to their own cross-over trial (5), both of which were included by Epstein et al. A meta-analysis covering stimulant and non-stimulant trials showed that cross-over trials resulted in a larger effect estimate compared to parallel-group trials (SMD = 0.51 versus SMD = 0.88, P value = 0.005) (6). Sensitivity analyses, where such trials are analysed separately, should have been conducted.

Third, 65% to 89% of adults with ADHD suffer from comorbid psychiatric conditions (7) and the exclusion of participants with psychiatric comorbidity leads to severely impaired external validity (8). Epstein et al. seem aware of the frequent occurrence of psychiatric comorbidity in the adult ADHD population as they listed associated comorbidities (p 5 ff.). Yet, they did not explore this aspect in the included trials. In comparison, we found that only two studies did not exclude participants with psychiatric comorbidity (Spencer 1995, Kooij 2004), whereas six studies did (Wood 1976, Mattes 1984, Wender 1985, Kuperman 2001, Tenenbaum 2002, Wender 2011), while this was unclear in three studies (Gualtieri 1985, Bouffard 2003, Spencer 2005). This should lead to additional downgrading for "Indirectness" according to GRADE, and the rating could therefore only be "very low".

Fourth, Epstein et al. acknowledged the negative impact of ADHD on "functional outcomes", such as job change frequency, work performance, traffic accidents, marital status and academic achievements. Yet, "functional outcomes" were not included as separate outcomes in the review. In our opinion, these functional outcomes are the most relevant for patients, peers and society.

Fifth, the trial duration was very short, one to seven weeks, and the long-term effects are therefore unknown. Epstein et al. acknowledged this, but it did not affect their conclusion or confidence in the evidence, although this should arguably lead to downgrading for "Indirectness". Most patients receive treatment for substantially longer periods of time and effects may diminish with increased treatment duration, as observed in the MTA study (9). Epstein et al. also confusingly reported treatment durations including the time after cross-overs and wash-out periods between crosses. For instance, Tenenbaum 2002 (10) was reported in the systematic review as lasting 14 weeks, but the active treatment phase was 3 weeks only.

Sixth, the total sample size in the review was 474, but 9 of 11 studies had between 8 and 45 participants. Such small samples sizes are often underpowered to detect a clinically relevant difference and may provide misleading effect sizes (11). One should perform sensitivity analyses and present a funnel plot to explore the risk of publication bias, but Epstein et al. abstained from such analysis since there were less than 10 trials for each outcome. A previous meta-analysis, however, found evidence of publication bias in trials of short-acting stimulants (P < 0.001) (6).

Seventh, Epstein et al. reported a combined effect size consisting of both self- and investigator-ratings, where the latter was preferred when both were reported in the trial. Previous meta-analyses have demonstrated substantial differences between self- and investigator-rated effect sizes with investigators estimating greater effects; Faraone et al. 2004 (SMD = 0.03 versus SMD = 1.1, P value = 0.02) and Faraone et al. 2010 (SMD = 0.43 versus SMD = 0.68, P value = 0.04) (6,12), something Epstein et al. seem aware of (p 6). Key

outcomes in this review are subjective, which compounds the problem. Sensitivity analyses, where the trials are analysed separately according to the type of rating (self and investigator), should have been conducted.

Eighth, Epstein et al. paid no attention to the problem of maintaining double-blind conditions with a stimulant drug without using an active placebo, despite their note about methylphenidate being "susceptible to detection" in double-blind trials (p 14). Nine of the 11 included studies used a titration scheme to achieve the highest tolerated dose. This method is likely to lead to poorer blinding, compared with a fixed-dose design. The adverse effects from taking a central stimulant will make blinding very unlikely to have been effective, even though the trials were described as "double-blind". As example of the ineffective blinding, it was reported by Gualtieri et al. that all eight participants in their trial were able to "break the code" and "accurately guess the active drug condition" (13).

Ninth, Epstein et al. wrote that pre-stated outcomes were reported in most included studies, and therefore judged the risk of outcome reporting bias as low (p 14). At the same time, they wrote in the abstract that: "We were unable to determine whether adverse effects were not discussed by study authors because none occurred or because no data on adverse effects were collected". They also noted that the lack of systematic reporting of harms prevented them from conducting meta-analyses of adverse events (p 20). However, this did not prevent them from concluding that: "Trial data suggest that adverse effects from immediate-release methylphenidate for adults with ADHD are not of serious clinical significance, although this conclusion may be limited, certainly in the case of weight loss, by the short duration of published studies". It is severely misleading to suggest that adverse effects are not of "serious clinical significance" when data are not available.

Tenth, Epstein et al. gave a narrative description of cardiovascular effects in five studies, but they did not conduct meta-analyses of pulse or blood pressure, which are the only meaningful cardiovascular outcomes in trials of such short duration. Mick et al. showed that CNS stimulants increase blood pressure and pulse in adults (14). This may increase the risk of ischaemic heart disease beyond the short follow-up period of the trials, particularly in an adult population where many have additional risk factors for cardiovascular disease.

Eleventh, Epstein et al. compared agreements and disagreements with three meta-analyses. They did not, however, compare their results with four newer meta-analyses by Koesters et al. (15), Faraone et al. (6), Castells et al. (16) and, in our opinion, the most comprehensive review about pharmacotherapy in ADHD by McDonagh et al. (1). The omission of such central references is problematic since these reviews reported different effect sizes and included analyses that Epstein et al. did not. McDonagh et al. considered the evidence of such poor reliability that they abstained from conducting meta-analyses.

The evidence does not allow firm conclusions on the efficacy or harms of immediate-release methylphenidate for adults with ADHD.

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Reply

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WHAT'S NEW

Last assessed as up-to-date: 27 April 2014.

Date	Event	Description
11 May 2016	Feedback has been incorporated	Four comments regarding methodological concerns and one comment regarding adverse effects

HISTORY

Protocol first published: Issue 4, 2004

Review first published: Issue 9, 2014

Date	Event	Description
23 August 2008	Amended	Converted to new review format
24 November 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Tamir Epstein: protocol writing, trial selection, data extraction and assimilation, statistical analysis, and review writing.

Mark Weiser: protocol writing, trial selection, data extraction and assimilation, statistical analysis, and review writing.

Nikolaos A Patsopoulos: statistical analysis and review writing.

DECLARATIONS OF INTEREST

Tamir Epstein has given talks on the diagnosis and treatment of adults with ADHD for Janssen, the manufacturer of Concerta.

Nikolaos A Patsopoulos worked as a consultant for Enhance Reviews Ltd from 2009 to 2010. Enhance Reviews is a private company that specializes in customized systematic reviews. He also served as a consultant for Merck, on an unrelated project.

Mark Weiser has given talks on the diagnosis and treatment of adults with ADHD for Janssen and Novartis, the manufacturers of Concerta and Ritalin LA.

Tamir Epstein and Mark Weiser often treat adults with ADHD using immediate-release methylphenidate.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- In our protocol, we stated that selection criteria would include randomized, placebo-controlled trials comparing immediate-release methylphenidate versus placebo in participants aged 18 years or older diagnosed with ADHD. We did not anticipate that some studies on this subject were designed and carried out specifically to examine the effects of methylphenidate on specific subpopulations of participants, such as those with ADHD and various substance abuse or dependence comorbidities, or those with ADHD and a diagnosis of traumatic brain injury. In a post hoc protocol change, we excluded trials conducted on subpopulations of adults with ADHD. We made this change because including such studies would obfuscate the clinical relevance of this review for both populations-those with substance or cognitive-influencing comorbidities, and those without. Therefore, we chose to exclude all studies explicitly designed to examine the efficacy of immediate-release methylphenidate for patients with psychiatric or neurological comorbidities.

- In our protocol, we stated that participants in the included studies would be 18 years of age or older and diagnosed with ADHD. However, some of the included studies examined participants aged 17 years or older (Spencer 1995; Bouffard 2003; Spencer 2005). None reported including participants younger than 17 years of age. We believe that excluding these studies would not have served the review's purpose and that their inclusion does not detract from the review's applicability for clinical practice.

- In our protocol, we stated that the types of interventions to be included were "1. Methylphenidate administered at any dosage, as part of any treatment regimen. 2. Placebo or non-intervention." Several methylphenidate-containing preparations are available, which, for various reasons (among them release extension and delivery method), may not have a similar effect. Therefore, we decided in a post hoc protocol change that the review would specifically focus on immediate-release methylphenidate.

- We rephrased our outcome measures and added a distinction between primary and secondary outcome measures that was not presented in our original protocol. We added the outcome of "overall change" as a secondary outcome measure. These changes were made for purposes of clarity.

- In our protocol, we stated that a fixed-effect model would be used. However in the review, a random-effects model was used for many outcomes. This change was made for several reasons. Upon reviewing the included studies, we found evidence of high statistical heterogeneity ($I^2 > 75\%$). A random-effects model allows for heterogeneity by assuming that underlying effects follow a normal distribution. In addition, results for the same outcomes were measured in various studies using different scales. The random-effects method incorporates an assumption that different studies are estimating different, yet related, intervention effects. We found this to be the case in the studies included in this review and therefore opted for the random-effects method.

INDEX TERMS

Medical Subject Headings (MeSH)

Attention Deficit Disorder with Hyperactivity [*drug therapy]; Central Nervous System Stimulants [adverse effects; *therapeutic use]; Methylphenidate [adverse effects; *therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Adult; Humans; Middle Aged