

Long-acting versus short-acting methylphenidate for paediatric ADHD: a systematic review and meta-analysis of comparative efficacy

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ABSTRACT

Objective: To synthesise existing knowledge of the efficacy and safety of long-acting versus short-acting methylphenidate for paediatric attention deficit hyperactivity disorder (ADHD).

Design: Systematic review and meta-analysis.

Data sources: Electronic literature search of CENTRAL, MEDLINE, PreMEDLINE, CINAHL, EMBASE, PsychINFO, Scopus and Web of Science for articles published in the English language between 1950 and 2012. Reference lists of included studies were checked for additional studies.

Study selection: Randomised controlled trials of paediatric ADHD patients (<18 years), comparing a long-acting methylphenidate form to a short-acting methylphenidate form.

Data extraction: Two authors independently selected trials, extracted data and assessed risk of bias. Continuous outcomes were compared using standardised mean differences (SMDs) between treatment groups. Adverse events were compared using risk differences between treatment groups. Heterogeneity was explored by subgroup analysis based on the type of long-acting formulation used.

Results: Thirteen RCTs were included; data from 882 participants contributed to the analysis. Meta-analysis of three studies which used parent ratings to report on hyperactivity/impulsivity had an SMD of -0.30 (95% CI -0.51 to -0.08) favouring the long-acting forms.

In contrast, three studies used teacher ratings to report on hyperactivity and had an SMD of 0.29 (95% CI 0.05 to 0.52) favouring the short-acting methylphenidate. In addition, subgroup analysis of three studies which used parent ratings to report on inattention/overactivity indicate that the osmotic release oral system generation long-acting formulation was favoured with an SMD of -0.35 (95% CI -0.52 to -0.17), while the second generation showed less efficacy than the short-acting formulation with an SMD of 0.42 (95% CI 0.17 to 0.68). The long-acting formulations presented with slightly more total reported adverse events ($n=578$) as compared with the short-acting formulation ($n=566$).

Conclusions: The findings from this systematic review indicate that the long-acting forms have a modest effect on the severity of inattention/overactivity and hyperactivity/impulsivity according to parent

ARTICLE SUMMARY

Article focus

- To systematically review and meta-analyse existing knowledge of the efficacy of long-acting versus short-acting methylphenidate for paediatric attention deficit hyperactivity disorder (ADHD).
- To systematically review existing knowledge of the safety of long-acting versus short-acting methylphenidate for paediatric ADHD.
- To help better inform clinical practice when treating children with ADHD.

Key messages

- Despite costing up to 15 times as much, long-acting methylphenidate preparations have modest effect on core symptoms based on parent reports, in comparison to short-acting preparations.
- Short-acting methylphenidate was slightly more favourable to core symptoms according to teacher reports.
- Both formulations present with similar adverse events.

Strengths and limitations of this study

Strengths

- Systematically reviewed a question that has never been reviewed and is clinically relevant.
- Search methods, data extraction and risk of bias assessment were thorough.

Limitations

- Only included studies published in English.
- Excluded grey literature.
- Did not include qualitative outcomes.

reports, whereas the short-acting methylphenidate was preferred according to teacher reports for hyperactivity.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in childhood, occurring in approximately 5.29% of children worldwide.¹

The core symptoms of ADHD (i.e., inattention, impulsivity and hyperactivity) can result in multiple areas of dysfunction relating to a child's performance in the home, school and community (American Academy of Pediatrics 2001). Furthermore, the core symptoms can be expressed to various degrees in different children, breaking ADHD into three subtypes: the predominantly inattentive type, the predominantly hyperactive-impulsive type and the combined type (ie, children displaying both inattention and hyperactivity).² The symptoms of ADHD have been shown to have long-term effects on a child's academic performance and social development. It has been estimated that up to 50–60% of childhood ADHD cases will persist into adulthood, making it a lifetime condition for many.^{3,4}

Stimulant medication is recommended as a first-line modality for treating ADHD.⁵ Evidence has suggested that ADHD may be the result of insufficient production of norepinephrine and dopamine in the prefrontal cortex,⁶ resulting in forgetfulness, distractibility, impulsivity and inappropriate social behaviours.⁷ By increasing the levels of norepinephrine and dopamine in the prefrontal cortex, stimulants are thought to restore executive functioning.⁶

Methylphenidate is the most commonly prescribed stimulant for children with ADHD. Numerous studies have shown that methylphenidate improves the core symptoms of ADHD as reflected in parent and teacher ratings.⁸ In the multimodality treatment study of ADHD⁹ a three-times daily regimen of immediate-release methylphenidate was selected as the gold standard pharmacological treatment of ADHD. Despite this, problems remain that are inherent to the multiple daily dosing including issues with adherence. As a result, a number of more expensive, extended-release formulations have been introduced into the market. First generation extended-release formulations utilise a wax-matrix to provide slow, continual release of methylphenidate;¹⁰ however, they have been found to have a slow onset of action. The second generation forms contain both immediate-release and extended-release coated particles, designed to have two phases of drug release resulting in rapid onset and longer durations ($t_{1/2}=6.8$ h). The final type of extended-release methylphenidate is the osmotic release oral system (OROS) methylphenidate, which is a controlled-release formulation that uses osmotic pressure to deliver methylphenidate at a controlled rate throughout the day ($t_{1/2}=6.4$ h).¹¹

To our knowledge, a systematic review comparing short-acting versus long-acting methylphenidate has never been conducted. As the long-acting formulations cost up to 15 times as much as the short-acting preparations,¹² we believe that establishing comparative efficacy and safety between the two forms is imperative. Thus, we conducted a systematic review and meta-analysis which includes a synthesis of all English published randomised controlled trials assessing the efficacy and safety of short-acting versus long-acting methylphenidate formulations to manage the core symptoms of paediatric ADHD.

METHODS

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PreMEDLINE, CINAHL, EMBASE and PsychINFO from 1950 to 1 August 2012. Relevant, published RCTs were identified using the key terms: *attention deficit with hyperactivity disorder, child/adolescent/paediatric, and methylphenidate*. English language restriction was applied. The reference lists of included studies identify additional studies.

Selection of studies

Selection of studies was based on a screening of titles and/or abstracts independently by two authors (SP and LZ). Both reviewers independently assessed the full-text articles of those studies whose inclusion was unclear, based on abstracts alone. Final decisions were reached by consensus, with disagreements being resolved by discussion.

Inclusion criteria

English published randomised controlled trials were selected if they met the following criteria: (1) participants were <18 years of age, with a clinical diagnosis of ADHD as determined by Diagnostic and Statistical Manual of Mental Disorders (DSM-III) (American Psychological Association (APA) 1987) or DSM-IV (APA 2000) criteria or equivalent (2) the trial compared a long-acting methylphenidate form with a short-acting methylphenidate form; and (3) the study measured either (a) efficacy defined as improvement of the core symptoms of ADHD (inattention, impulsivity, hyperactivity) measured by either parent and/or teacher rating scales; or (b) adverse events.

Data extraction

Two authors (SP and LZ) independently extracted data from the selected studies using data extraction forms. Extracted data included patient demographics, interventions used, outcomes and trial design. Discrepancies were resolved by discussion; however, there were no major differences in extraction between the review authors.

Missing data

Authors were contacted up to three times to obtain missing data. Clarification was required by one of the authors as to who had filled out the ADHD symptom questionnaire, but no response was provided.

Risk of bias assessment

Two authors (SP and LZ) independently assessed the risk of bias of each trial, following the domain-based evaluation as described in the Cochrane Handbook for Systematic Reviews of Interventions 5.0.0.¹³ Six domains were assessed: randomisation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. Disagreements between the authors were resolved by discussion.

Outcomes

The outcomes of interest included efficacy and adverse events. Efficacy was defined as improvement of the core symptoms of ADHD (inattention, impulsivity, hyperactivity) measured by parent and/or teacher rating scales. Secondary outcomes included adverse events.

Statistical analysis

Continuous outcomes (ie, change in core symptoms) were recorded as the mean relative changes from baseline (where possible) or mean end-point values and SD. Meta-analysis was conducted for each core symptom that was reported in more than one study. Since the scales differed across the studies, the effect size was calculated using standard mean differences (SMD) and 95% CI. We employed a random-effects model for all analyses.

For crossover trials, endpoints of both periods were combined for each treatment arm. For studies with multiple treatment arms, only the relevant intervention arms were taken into consideration.

We measured the inconsistency of study results using the I^2 heterogeneity statistic to determine if the variation in outcomes across trials was due to study heterogeneity rather than chance (Higgins 2011). I^2 values of 25% indicate low heterogeneity, 50% indicate moderate heterogeneity and 75% indicate high heterogeneity.¹³ Heterogeneity was further explored by subgroup analysis (discussed below).

Subgroup analyses

Where I^2 was found to be >50%, we performed subgroup analyses based on the type of long-acting formulation used.

Sensitivity analysis

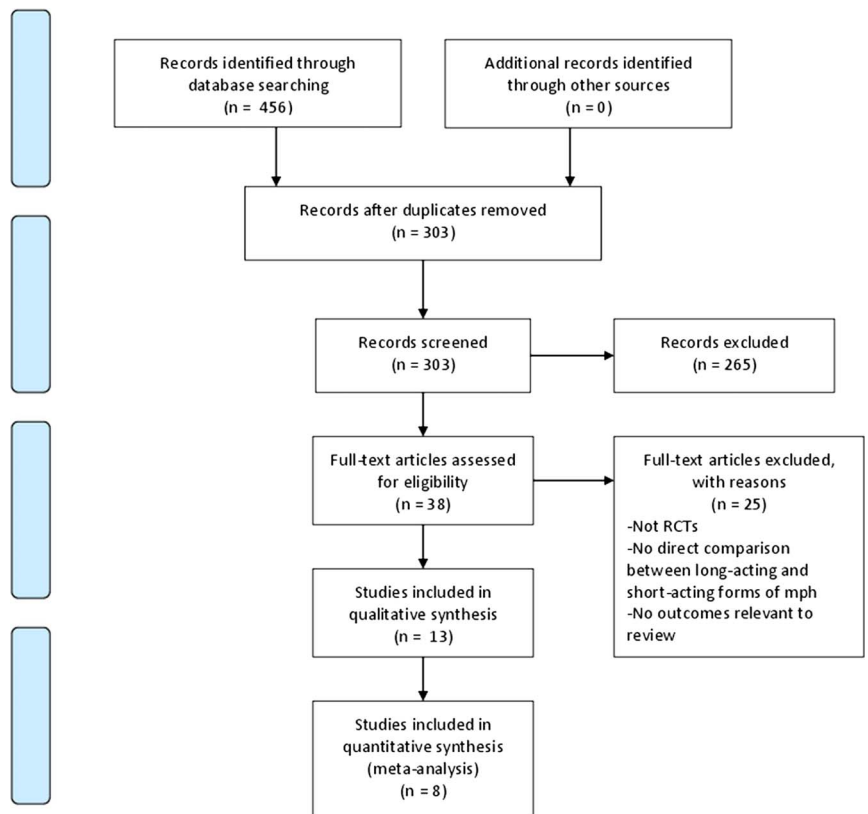
A sensitivity analysis based on risk of bias using only studies rated with a low-risk of bias in all six domains of the risk of bias tool was planned; however, since no study met this requirement, this analysis was not conducted.

All calculations were performed using the Cochrane Collaboration’s Review Manager Software (RevMan 2008).

RESULTS

The search of the electronic databases retrieved 456 publications. After eliminating duplicates, 303 publications were identified for further consideration. After screening the titles and available abstracts, 38 studies were considered for possible inclusion. Of those 38 studies, 13 met criteria for inclusion in the view.^{10 14–25} The flow of studies through the screening process of the review is shown in figure 1 and are reported based on the PRISMA guidelines.²⁶ The 13 eligible studies included 8 crossover RCTs and 5 parallel RCTs. The number of participants per study ranged between 13 and 272, with a total of 1031 participants. The average age of the participants of the included studies ranged from 8.25 to 11.3 years. Four studies used first generation long-acting methylphenidate, five studies used the

Figure 1 PRISMA flow diagram.



second generation formulation and four studies assessed OROS methylphenidate. Characteristics of the included studies can be found in [table 1](#).

Risk of bias

Trials consistently failed to describe sequence generation and allocation concealment, resulting in a mostly unclear risk of bias assessment with respect to those domains. Most trials sufficiently described their blinding methods and addressed their incomplete data. It was not possible to assess for selective reporting, as protocols were not made available for any of the studies. The area where the majority of trials were assessed as having a high risk of bias was in the 'other sources of bias' domain, owing to sources of funding. Ten studies reported that they were affiliated with or funded by industry.^{10 15 17-21}

Meta-analysis

Primary outcomes

Ten studies reported on the core symptoms of ADHD.^{14 16-22 24 25} Most studies used both parent and teacher reports to assess symptoms, except Steele *et al*, who used only parent reports, and Dopfner *et al*, who used only teacher reports ([figure 2](#)).^{19 22} The study results of Dopfner *et al* could not be included in the meta-analysis since the study was conducted over a single day. The study results of Schachar *et al* could not be included in the meta-analysis because the study did not specify who had completed the questionnaire.

Inattention/overactivity (a) Teacher reports: four studies used teacher ratings to report inattention/overactivity.^{16-18 20} The meta-analysis showed no significant differences between the short-acting and long-acting forms (SMD of -0.04 (95% CI -0.31 to 0.23)). (b) Parent reports: five studies used parent ratings to report inattention/overactivity.^{16-18 20 22} The meta-analysis revealed no significant differences between the methylphenidate formulations; however, heterogeneity was high at 83%. Subgroup analysis was conducted by the type of long-acting formulation (1st generation vs 2nd generation vs OROS generation) and found significant differences between the short-acting and long-acting forms of methylphenidate in the second and OROS generation subgroups. The second generation subgroup favoured short-acting methylphenidate with an SMD of 0.42 (95% CI 0.17 to 0.68), while the OROS generation subgroup favoured the long-acting form, with an SMD of 0.35 (95% CI -0.52 to 0.17).

Inattention (a) Teacher reports: four studies used teacher ratings to report inattention.^{14 18 21 24} The meta-analysis revealed no significant differences between formulations (SMD 0.07 (95% CI -0.11 to 0.24)). (b) Parent reports: three studies used parent ratings to report inattention^{18 21 24} and the pooled results showed no significant difference (SMD -0.12 (95% CI -0.31 to 0.06)).

Hyperactivity (a) Teacher reports: three studies used teacher ratings to report hyperactivity.^{14 16 24} The

meta-analysis showed significant results in favour of the short-acting form, with an SMD of 0.29 (95% CI 0.05 to 0.52) ([figure 2B](#)). (b) Parent reports: two studies used parent ratings to report hyperactivity,^{16 24} and the meta-analysis revealed no significant differences between methylphenidate formulations (SMD -0.01 (95% CI of -0.28 to 0.25)).

Hyperactivity/Impulsivity (a) Teacher reports: two studies used teacher ratings to report hyperactivity/impulsivity.^{18 21} The meta-analysis revealed no significant difference between short-acting and long-acting formulations (SMD -0.00 (95% CI -0.24 to 0.24)). (b) Parent reports: three studies used parent ratings to report hyperactivity/impulsivity.^{14 18 21} The meta-analysis revealed significant results favouring the long-acting form, with an SMD of -0.31 (95% CI -0.51 to -0.08).

Adverse events

Twelve of the 13 included studies reported on adverse events;^{14-18 20-25} however, one of these studies did not provide clear numbers of adverse events.¹⁴ Forty-two adverse events were extracted from 11 studies, of which the most commonly reported adverse events included anorexia, headaches, abdominal pain and insomnia in both formulations (see [table 2](#)). The long-acting formulations presented with slightly more total reported adverse events (n=578) as compared with the short-acting formulations (n=566).

DISCUSSION

While the therapeutic effect of short-acting methylphenidate has been well established, the introduction of more expensive, long-acting formulations in the market makes comparative effectiveness and safety paramount. The findings from this systematic review indicate that the long-acting forms have a modest effect on the severity of inattention/overactivity and hyperactivity/impulsivity according to parent reports, whereas the short-acting methylphenidate was preferred according to teacher reports for hyperactivity. These discrepancies between parent and teacher ratings may reflect differing demands between home and school environments; therefore, determining the environment in which a child's ADHD symptoms most affect them may help guide appropriate treatment decisions.

While our study demonstrates a slight preference towards the long-acting or short-acting methylphenidate on certain core symptoms, depending on the environment, we recognise that our results depend on the internal validity of the included studies. Not one of the included primary studies had a low risk of bias rating on all domains of the Cochrane risk of bias tool, which can result in overestimates of treatment effect.²⁷ In addition, we are unable to examine claims regarding the comparative efficacy of long-term use of these formulations (ie, beyond 8 weeks use). Twelve studies were of only 4 weeks duration; only one evaluated treatment effect at 8 weeks.

Table 1 Characteristics of included studies

Study, year of publication	Country where study was conducted	Sample size (% male)	Age (Mean (SD))	Study design	Duration of intervention	Long-acting formulation generation	Relevant outcomes	Rating scale(s) used for core symptoms
Whitehouse, 1980	USA	30 (83)	8.5*	Parallel	14 days	1st generation	Core symptoms: Inattention Hyperactivity Hyperactivity/Impulsivity Adverse events	(i) Parent-Rating Scale† (ii) Teacher-Rating Scale†
Pelham, 1987	USA	13 (100)	8.8 (1.5)	Crossover	Not reported	1st generation	Adverse events	N/A
Pelham, 1990	USA	22 (100)	10.39 (1.38)	Crossover	3–6 days	1st generation	Adverse events	N/A
Fitzpatrick, 1992	USA	19 (89)	8.72 (1.33)	Crossover	14 days/period	1st generation	(i) Core symptoms: Hyperactivity Inattention/overactivity (ii) Adverse events	(i) IOWA Conners' Parent Rating Scale (ii) IOWA Conners' Teacher Rating Scale
Pelham, 2001	USA	70 (89)	9.1(1.6)	Crossover	7 days/period	OROS	(i) Core symptoms: Inattention/overactivity (ii) Adverse events	(i) IOWA Conners' Parent Rating Scale (ii) IOWA Conners' Teacher Rating Scale
Wolraich, 2001	USA	192 (82)	9.0(1.8)	Parallel	28 days	OROS	(i) Core symptoms: Inattention Inattention/ overactivity Hyperactivity/impulsivity (ii) Adverse events	(i) IOWA Conners' Parent Rating Scale (ii) IOWA Conners' Teacher Rating Scale (iii) Parent SNAP-IV (iv) Teacher SNAP-IV FBB-HKS Teacher Rating Scale
Dopfner, 2004	Germany	79 (90)	10(1.6)	Crossover	4–6 days/period	2nd generation	Core symptoms: Inattention Hyperactivity/ impulsivity	
Findling, 2006	Australia, Canada, USA	272 (80)	9.5(1.73)	Parallel	21 days	2nd generation	(i) Core symptoms: Inattention/overactivity (ii) Adverse events	(i) IOWA Conners' Parent Rating Scale (ii) IOWA Conners' Teacher Rating Scale
Gau, 2006	Taiwan	64 (91)	10.5(3.2)	Parallel	28 days	OROS	(i) Core symptoms: Inattention Hyperactivity/impulsivity (ii) Adverse events	(i) Chinese version of the Conners' Parent Rating Scale Revised (ii) Chinese version of the Conners' Teacher Rating Scale Revised IOWA Conners' Parent Rating Scale
Steele, 2006	Canada	145 (83)	8.25(2.1)	Parallel	56 days	OROS	(i) Core symptoms: Inattention/Overactivity (ii) Adverse events	
Quinn, 2007	Canada	18 (72)	9.6(2.5)	Crossover	1 day/period	2nd generation	Adverse events	N/A
Weiss, 2007	Canada	90 (91)	11(2.5)	Crossover	14 days/period	2nd generation	(i) Core symptoms: Inattention Hyperactivity (ii) Adverse events	(i) Conners' Parent Scale Revised (ii) Conners' Teacher Scale Revised
Schachar, 2008	Canada	17 (88)	11.3(2.2)	Crossover	7 days/period	2nd generation	(i) Core symptoms: Inattention/overactivity (ii) Adverse events	IOWA-C‡

*No SD reported.

†Study did not specify which scales were used.

‡Study did not specify who completed the questionnaire.

IOWA-C, Inattention/Overactivity with Aggression Conners' scale; N/A, not applicable; OROS, osmotic release oral system.

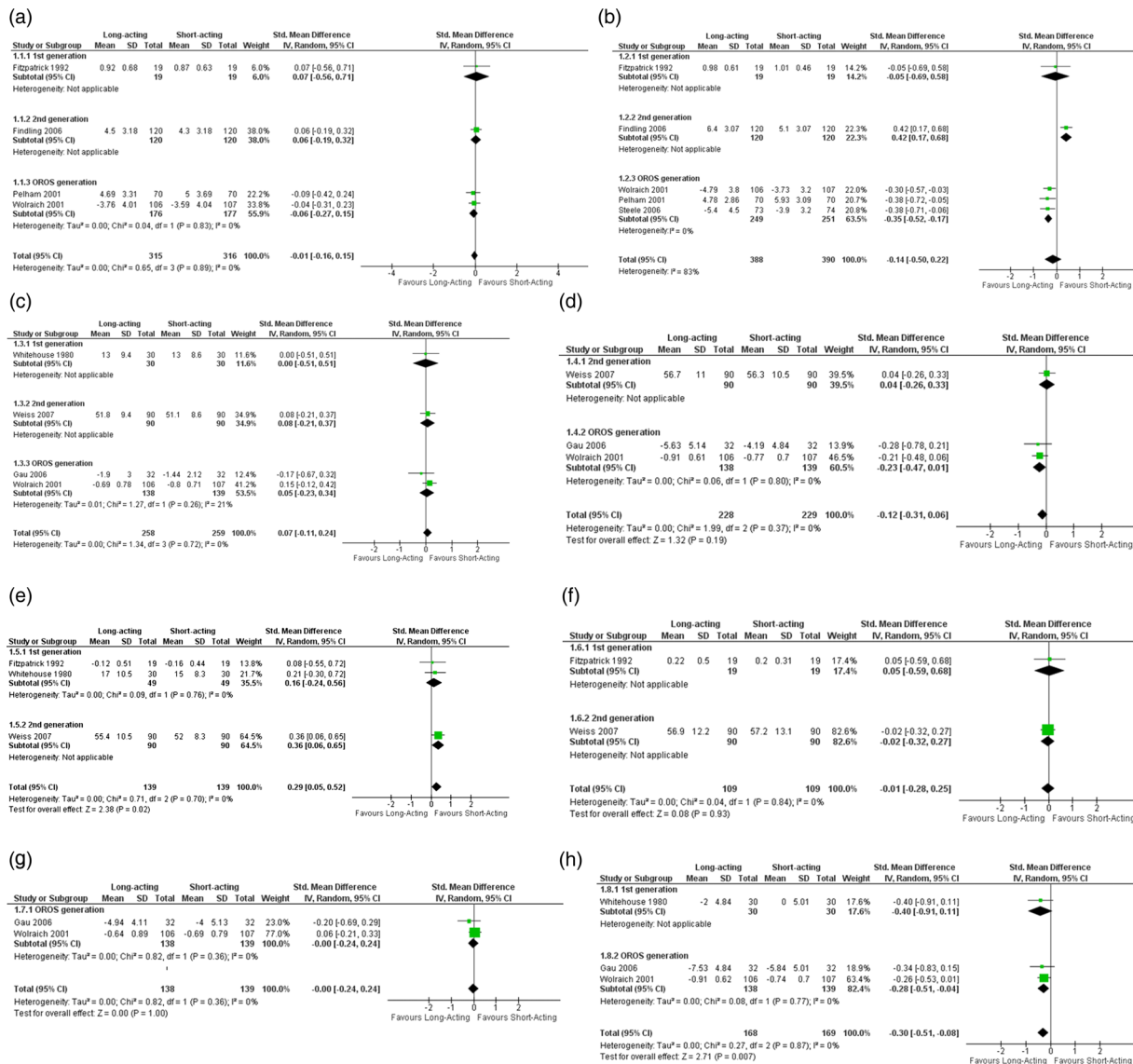


Figure 2 (A) Teacher reports: inattention/overactivity meta-analysis. (B) Parent reports: inattention/overactivity meta-analysis. (C) Teacher reports: inattention meta-analysis. (D) Parent reports: inattention meta-analysis. (E) Teacher reports: hyperactivity meta-analysis. (F) Parent reports: hyperactivity meta-analysis. (G) Teacher reports: hyperactivity/impulsivity meta-analysis. (H) Parent reports: hyperactivity/impulsivity meta-analysis.

Short trials are particularly problematic in a chronic condition such as ADHD, as children receive stimulant medications for much longer time periods than what was studied in these trials. In addition, the results of our review may have been influenced by the inclusion of several studies affiliated with or funded by pharmaceutical companies. This has been shown to be strongly associated with an overestimate of treatment effect in favour of the sponsor's interest, thereby potentially distorting the true measures of outcome in this review.²⁸

Our review found no difference in the reported adverse events between the two formulations, but this warrants cautious interpretation. The included studies were powered to assess efficacy, not safety, so the lack of statistical difference between groups is not surprising. We also found that adverse event reporting was often

unclear among the primary studies. For example, some studies only reported on adverse events that were experienced by a certain percentage of the participants within their trial, thereby ignoring any adverse events reported by less than that fraction. Moreover, studies were unclear about how and when they ascertained adverse events, and whether they were associated with the interventions themselves. Heterogeneous terms used to describe adverse events also limited our ability to meaningfully synthesise the adverse event data, which limits its utility. Finally, as with efficacy data, long-term safety data are not available because of the paucity of long-term trials.

Limitations of our review include not including grey literature in our search, which would exclude unpublished work. Since published trials are known to describe a larger treatment effect than unpublished trials,²⁹

Table 2 Adverse events extracted from each study

Adverse event	No. of studies	Long-acting methylphenidate		Short-acting methylphenidate		Risk difference
		No. of events	Sample size	No. of events	Sample size	
Central nervous system						
Abnormal behaviour	1	4	139	3	133	0.006
Agitation	1	8	73	5	74	0.042
Anger	1	6	19	2	19	0.211
Anorexia	9	135	553	124	550	0.019
Anxiety/nervousness	4	31	217	35	218	-0.018
Bites fingernails	2	7	54	9	54	-0.037
Cries easily	2	5	41	4	41	0.024
Distorted vision	1	0	22	0	22	0
Dull/withdrawn	2	10	54	18	54	-0.148
Emotional lability	2	12	163	8	164	0.025
Euphoric	1	5	32	3	32	0.063
Fainting/dizziness	2	2	92	1	92	0.011
Fatigue, drowsiness	4	22	217	13	218	0.042
Fever	1	4	139	1	133	0.021
Grabby, touchy	1	2	22	0	22	0.091
Headache	9	74	543	60	540	0.025
Hyperphagia	2	4	209	7	203	-0.015
Insomnia/sleep problems	5	57	356	53	351	0.009
Irritable/whiny	4	8	210	15	204	-0.035
Nightmares	2	5	54	8	54	-0.055
Sad, unhappy	5	20	180	25	180	-0.028
Shakiness	2	0	41	0	41	0
Stares, daydreams	1	9	32	10	32	-0.031
Talks less	1	8	32	9	32	-0.031
Tics	6	11	426	18	422	-0.017
Weakness	1	1	22	0	22	0.045
<i>Subtotal for central nervous system</i>		<i>450</i>		<i>431</i>		
Gastrointestinal						
Abdominal pain/stomach ache	9	57	558	62	555	-0.010
Diarrhoea	1	0	70	2	70	-0.029
Dry mouth	3	11	73	12	73	-0.014
Dyspepsia	1	1	18	1	18	0
Vomiting, nausea	7	21	375	15	369	0.015
<i>Subtotal for gastrointestinal</i>		<i>90</i>		<i>92</i>		
Respiratory						
Cough	1	2	139	4	133	-0.016
Flu-like/viral symptoms	3	7	234	7	229	-0.001
Pharyngitis	3	14	227	8	221	0.039
Rhinitis	2	6	209	11	203	-0.025
<i>Subtotal for respiratory</i>		<i>29</i>		<i>30</i>		
Other						
Accidental injury	1	1	70	3	70	-0.029
Muscle aches	1	1	22	2	22	-0.045
Polydipsia	1	1	19	0	19	0.053
Pruritus	1	1	18	0	18	0.056
Rash	1	0	139	0	133	0
Rebound effects	1	5	90	6	90	-0.011
Urinary incontinence	2	0	92	2	92	-0.022
<i>Subtotal for other</i>		<i>9</i>		<i>13</i>		
Total		578		566		

excluding grey literature may result in an over-estimate of treatment effect. We did not report on indirect outcomes, such as quality of life, social functioning, academic achievement or patient preference. While these indirect outcomes are impacted by ADHD,³ our primary interest was the effect of the two medication classes on the core symptoms of ADHD, since this is the reason they are prescribed. We also chose not to include physician or child self-report regarding core symptom assessment, thereby excluding potentially important perspectives on treatment effect. Instead, we chose parents and teachers as guidelines identify their perspective as being the most important to clinicians and researchers regarding a child's naturalistic functioning in relation to peers of the same age and sex.^{30 31}

Future trials should assess the long-term comparative effectiveness and safety of ADHD stimulant medications. Although issues with compliance are a primary motivation to use long-acting medications, only three studies reported compliance. While one supports greater compliance in those taking the long-acting formulation (Steele *et al*), the other two found no difference in compliance between the two formulations (Pelham 2001, Schachar *et al*). Future studies should report compliance in order to allow determination of the cost-to-benefit ratio of long-acting versus short-acting formulations. It would also be helpful if future studies separated ADHD subtypes in their analyses, in order to note important differences in treatment effects, and reported all adverse events in all participants, to allow for more meaningful data synthesis. Future research should take into account not only symptom management but also global outcomes and patient preference.

Based on the findings of this review, neither long-acting or short-acting forms of methylphenidate alleviate all core symptoms of ADHD across both home and school environments. Long-acting formulations can cost up to 15 times more than the generic short-acting formulation, without evidence of greater compliance. For children whose ADHD symptoms are impacting their school performance, parents and healthcare providers can be confident that short-acting methylphenidate will be found to be effective by teachers. Further research is needed to investigate the long-term costs, benefits, and harms of both formulations of methylphenidate in ADHD patients of all sub-types.

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Contributors SP and SV conceived this review. SP led the design and ongoing coordination of this review with oversight from SV. SP developed the additional search strategies and carried out the searches for this review. SP organised the retrieval of papers for this review. SP and LZ screened the retrieved papers against inclusion criteria for this review. SP and LZ settled disagreements regarding the included studies for this review through discussion. SP and LZ independently appraised the quality of papers for this review. SP and LZ independently extracted data from papers for this review. SP wrote to the authors of the included studies for additional information for this review. SP managed data for this review including entering data into

RevMan and analysing the data with the assistance of Ben Vandermeer. SP interpreted the data for this review. SP wrote the review. JN, LH, LU, LZ and SV critically read and edited the review prior to submission.

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