Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents
assessment of harmful effects in non-randomised studies

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Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents - assessment of harmful effects in non-randomised studies (Protocol)


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Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents - assessment of harmful effects in non-randomised studies (Protocol)

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Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents - assessment of harmful effects in non-randomised studies

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the harmful effects of methylphenidate treatment for children and adolescents with attention deficit hyperactivity disorder (ADHD) in non-randomised studies.
BACKGROUND

Description of the condition

Attention deficit hyperactivity disorder (ADHD) is one of the most commonly diagnosed and treated childhood psychiatric disorders (Scahill 2000). The estimated prevalence in children and adolescents is between 3% and 5% (Polanczyk 2007), depending on the classification system used, with boys two to four times more likely to be diagnosed than girls (Schmidt 2009). Prevalence rates have remained stable over the past 30 years and do not appear to vary between countries (Polanczyk 2014). Individuals with ADHD show difficulties in attention and cognitive functions, for example, problem-solving, planning, orienting, flexibility, response inhibition, and working memory (Pasini 2007; Sergeant 2003). Children and adolescents also have high rates of problems involving affective components such as motivational delay and mood dysregulation (Castellanos 2006; Nigg 2005; Schmidt 2009).

Many studies have examined environmental risk factors for ADHD development, however, no specific factor seems to predict who is and is not at high risk of developing ADHD. At the population level, poverty (families living under the poverty level) is more likely to be a feature among American children and adolescents diagnosed with ADHD (CDC 2015). In a Swedish cohort of 811,803 individuals, low family income in early childhood was highly associated with ADHD (Larsson 2014). Low birth weight (Indredavik 2004; Van Lieshout 2015), prematurity (Bhutta 2002; Burnett 2014; Elgen 2015), maternal exposure to tobacco (Kovess 2015; Obel 2015), and chemical components like lead (Hong 2015) and manganese (Hong 2014) remain questionable risk factors for ADHD development. To be diagnosed with ADHD, a child must display, before 12 years of age, excessive inattentiveness, hyperactivity and impulsivity that impairs his/her functioning or development (APA 2013; WHO 1992). There are 18 symptoms of ADHD according to the principal diagnostic classification systems: the International Classification of Diseases Tenth Revision (ICD-10; WHO 1992), and the Diagnostic and Statistical Manual of Mental Disorders (DSM) Fourth Edition (DSM-IV; APA 1994); Fourth Edition, Text Revision (DSM-IV-TR; APA 2000); and Fifth Edition (DSM-5; APA 2013).

The DSM-5 and ICD-10 criteria require that the inattention, hyperactivity, and impulsivity are pervasive (for example, maladaptive symptoms of hyperactivity-impulsivity or inattention that are present at home and at school, before 6 (ICD-10; WHO 1992) or 12 (DSM-5; APA 2013) years of age, and that persist for at least 6 months. There must also be clear evidence of clinically-significant impairment in social, academic, and occupational functioning (APA 1994; APA 2000; WHO 1992). The diagnostic criteria set out in the DSM-IV and DSM-5 divide ADHD into three different subtypes each with their own particular set of symptoms: 'predominantly inattentive type', the 'predominantly hyperactive-impulsive type', and the 'combined type' - a combination of both hyperactive-impulsive and inattentive symptoms (APA 2013; Willcut 2012).

Children, adolescents and adults with ADHD are at increased risk of a broad spectrum of comorbid psychiatric disorders, which frequently result in negative outcomes later in life (Newcorn 2008; Schmidt 2009). The Multimodal Treatment of Attention Deficit Hyperactivity Disorder (MTA) trial identified one or more comorbid disorders in almost 40% of the participants (MTA 1999). These included oppositional defiant disorder, conduct disorder, depression, anxiety, tics, learning disorders, and verbal and cognitive difficulties (Jensen 2001; Kadesjö 2001). More recently, studies have confirmed such comorbidity (Czamara 2013; Yoshimasu 2012), and noted that excess weight and obesity (Cortese 2016) are found with ADHD. Depending on the severity, the presence of these comorbid conditions may modify the medication treatment, adding new classes of medications.

Description of the intervention

Stimulant medications, notably methylphenidate, dexamphetamine and atomoxetine (a non-stimulant selective noradrenaline reuptake inhibitor), are considered treatments of choice for children and adolescents with ADHD (Greenhill 2006; NCCMH 2009b; Pliszka 2007). The decision regarding which product to use is based upon a range of factors, including types of comorbid disorders, adverse events associated with the drug, issues regarding compliance, the potential for drug diversion and the preference of the child/adolescent and/or parents of the child. (Note, we use the term 'adverse events' to describe any harms, adverse effects or adverse drug reactions associated with methylphenidate). Very often psychological treatment is recommended as a part of the treatment, or even used before drug treatment (AAP 2011; Bolea-Alamañac 2014; NCCMH 2009a; Taylor 2004). Globally, methylphenidate is the most commonly used drug to treat ADHD; it has been used in practice for more than 50 years (Kadesjö 2002; NCCMH 2009b).

Methylphenidate is used because it appears to have a favourable effect on the major symptoms of hyperactivity, impulsivity, and inattention in children and adolescents with ADHD. However, a new Cochrane review investigating the effects of methylphenidate for children and adolescents with ADHD reported that it was not possible to demonstrate that methylphenidate offers more benefits than harms compared to placebo or no treatment (Storebø 2015). The dose of methylphenidate varies from patient to patient, with some children responding to relatively low doses and others requiring higher doses. The dose needs to be titrated individually in order to maximise benefits and minimise any potential adverse events (Stevenson 1989). It is often titrated according to weight, with smaller children receiving lower doses. The therapeutic range of methylphenidate dosages usually varies from 5 mg to 60 mg.
administered one to three times daily, depending on the release system and mode of administration (Pliszka 2007; Storebø 2015).

How the intervention might work

It is presumed that the effects of methylphenidate on ADHD symptoms are related to its effects on dopaminergic and noradrenergic neurotransmissions in the central nervous system (CNS) (Engert 2008). Methylphenidate is thought to act primarily as a dopamine-norepinephrine reuptake inhibitor, thereby increasing the availability of dopamine and norepinephrine (Heal 2006). The bioavailability of oral methylphenidate is 11% to 52%, with an approximate duration of action of 2 to 4 hours for immediate-release methylphenidate, 3 to 8 hours for sustained-release methylphenidate, and 8 to 12 hours for extended-release methylphenidate (Kimko 1999). Methylphenidate is believed to improve function (through symptom control) via dopaminergic pathways (Barkley 1977; Schulz 2012; Solanto 1998). This may improve classroom functioning and academic learning (Biederman 2003; Cox 2004; Evans 2001; Swanson 2004; Yang 2004). Methylphenidate has also been shown to reduce harmful secondary outcomes. For example, in an extensive cohort of 710,120 individuals, including 4557 individuals diagnosed with ADHD before 10 years of age, the use of methylphenidate was found to reduce emergency department visits by 45.7% and injuries by 43.5% (Dalsgaard 2015a).

The mechanism of action of methylphenidate is not clearly understood, but it probably works by blocking the norepinephrine and dopamine transporters in the synaptic cleft. This action interrupts neurotransmitter reuptake, increasing dopamine concentration in the cleft (Volkow 1998; Volkow 2004). As a result, patients can experience several benefits such as improved attention and reduced hyperactivity-impulsivity (Barkley 1981; Barkley 1989; Connor 2002; Shaw 2012). However, given the lack of sufficiently powered, well conducted randomised clinical trials (RCTs), it is not clear if these are genuine benefits or statistical artefacts (Storebø 2015). In a positron emission tomography (PET) study with 16 healthy participants, Volkow 2004 demonstrated that methylphenidate enhanced motivation for cognitive exercises - following treatment, participants rated the tasks as more interesting and motivating. In a similar vein, Schweizer 2004 found that methylphenidate can enhance performance by filtering out distractions in patients with ADHD. Other research has demonstrated that the accumulation of dopamine after blockade by methylphenidate is greater in more inattentive and impulsive patients, implying that methylphenidate could benefit those with more severe symptoms (Rosa-Neto 2005). A recent study demonstrated that methylphenidate increases dopamine in ventral striatum and prefrontal and temporal cortices, decreasing rates of inattention (Volkow 2012). In addition, the authors hypothesised that chronic methylphenidate use may result in adaptations in dopamine striatal signalling.

In a supplementary analysis of the study “A Comparison of Methylphenidates in an Analog Classroom Setting” (COMACS), the investigators found that girls responded to methylphenidate better than boys (Sonuga-Barke 2007; Swanson 2004). Barkley 1991 also found differences in response to methylphenidate between ADHD inattentive and combined subtypes.

Why it is important to do this review

The most common reported adverse events associated with methylphenidate are headache, sleep problems, tiredness, and decreased appetite. Some studies have indicated that methylphenidate also impairs children’s height and weight (Schachar 1997; Swanson 2004; Swanson 2009). In addition, there have been reports of sudden death among adults taking methylphenidate for the treatment of ADHD, but more research is needed to determine whether these deaths are related to methylphenidate (U.S. FDA 2011). A recent register-based Danish study of children and adults with ADHD has shown that children with ADHD do have a higher mortality rate compared to children and adults without ADHD; however, the role of ADHD medications in this apparent increase in mortality was not investigated (Dalsgaard 2015b). Because of the limitations of identifying and reporting adverse events in RCTs, particularly with low prevalence and longer-term effects (Storebø 2015), it is appropriate to synthesise data on adverse events from non-randomised studies. These data can help children and their families, clinicians and policy-makers make better decisions on the relative risks and benefits, as well as treatment acceptability, of methylphenidate (Catalá-López 2013; Donnelly 2004; Hong 2009; King 2006).

Over the last 15 years, several reviews have investigated the efficacy of methylphenidate for ADHD. Most of the reviews have investigated the effects of methylphenidate on beneficial outcomes, predominantly with regard to the symptoms of ADHD, and not potential harms (Storebø 2015). Due to the limitations of existing reviews, we conducted a comprehensive Cochrane systematic review investigating the short-term benefits and harms of methylphenidate for children and adolescents. We found evidence to suggest that methylphenidate may have a small beneficial effect on ADHD symptoms, general behaviour and quality of life (Storebø 2015). We also found evidence that methylphenidate is not associated with an increased risk of serious adverse events in the short term, but is associated with a relatively high risk of serious adverse events in general. However, the quality of the evidence included in the review was very low to low, due to a number of limitations, including lack of blinding in spite of placebo use, outcome reporting bias, and heterogeneity. Furthermore, the trials were generally of short duration, with a mean follow-up of just over two months, and thus not well suited to detecting rare or insidious adverse reactions, and so there is a need to investigate possible long-term harms in non-randomised studies (Storebø 2015).
The advantages of non-randomised studies, compared to RCTs, in collecting information on adverse events are that they can be much bigger, allowing for detection of rare adverse events, and participants can also be followed up for much longer periods, allowing for detection of late adverse events. On the other hand, the disadvantage of non-randomised studies compared to RCTs is the lack of a placebo (or nocebo) comparator, which means that any apparent association between the intervention and the observed harmful effect may be related to other factors.

**OBJECTIVES**

To assess the harmful effects of methylphenidate treatment for children and adolescents with attention deficit hyperactivity disorder (ADHD) in non-randomised studies.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

We will include only the following non-randomised study designs (Higgins 2011).

1. Cohort studies.
2. Case-control studies.
3. Follow-up periods from RCTs and case studies.

For a description of cohort and case-control studies see Table 1.

**Types of participants**

Children and adolescents up to and including 18 years of age with an intellectual quotient (IQ) greater than 70, with ADHD, with or without comorbid conditions.

We will accept the following diagnoses of ADHD:


**Types of interventions**

Methylphenidate administered at any dosage or formulation as part of any medical treatment regimen.

**Types of outcome measures**

**Primary outcomes**

Number of serious adverse events, defined as any event that leads to death or is life-threatening, or that requires inpatient hospitalisation or prolongation of existing hospitalisation, or that results in persistent or significant disability, or any other important medical event that may jeopardise the patient's life, or any event that requires intervention to prevent any of these outcomes.

**Secondary outcomes**

All other adverse events, including but not confined to the following types of events/effects: cardiological, neurological, gastrointestinal, sleeping problems, and growth retardation according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R1) (ICH 1996).

Adverse events could be measured during treatment, at the end of treatment, and at the longest follow-up, using rating scales, spontaneous reports recorded by the investigators at regular interviews or visits, and physical examinations or para-clinical examinations.

We will report ‘total adverse events’, separated into ‘serious’ and ‘other’, as defined above, in the ‘Summary of findings’ table. We will also report in this table, up to five additional adverse events that demonstrate the largest estimated difference between the methylphenidate group and the control group as well as those with the highest prevalence.

**Search methods for identification of studies**

**Electronic searches**

We will search the following electronic databases to identify relevant studies.

1. Cochrane Central Register of Controlled Trials (CENTRAL; current issue; part of the Cochrane Library) and which includes the specialised register of the Cochrane Developmental, Psychosocial and Learning Problems Group.
2. Ovid MEDLINE (1948 to current).
3. EMBASE (1980 to current; Ovid).
4. PsycINFO (1806 to current; Ovid).
5. CINAHL (Cumulative Index to Nursing & Allied Health Literature; 1980 to current; EBSCOhost).
6. Conference Proceedings Citation Index - Science (CPCI-S; 1990 to current; Web of Science).
7. Conference Proceedings Citation Index - Social Science & Humanities (CPCI-S&H; 1990 to current; Web of Science).
8. NDLTD (ndltd.org/resources; all available years).
9. Clinical Trials.gov (Clinical Trials.gov; all available years).
10. World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP; who.int/ictrp/en; all available years).

Since we will include data from follow-up periods from RCTs, and also from non-randomised studies, we will use two different search strategies, one for efficacy and one for adverse events of methylphenidate. We will not limit our searches by language, year of publication, or type of publication. We will seek translations of the relevant sections of non-English language articles. The search strategies for Ovid MEDLINE are in Appendix 1, and will be adapted for the other sources.

Searching other resources
To find additional relevant trials not identified by electronic searches, we will check the reference lists of other relevant reviews, meta-analyses and studies. We will also contact responsible parties of trials and pharmaceutical companies for data by email. Finally, we will search for unpublished data on the websites of the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

Data collection and analysis
We will conduct the review according to the Cochrane Handbook for Systematic Reviews of Interventions and PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (Higgins 2011; Liberati 2009; Moher 2015), and according to the guidelines in A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI; Sterne 2014). We will perform the analysis using the software, Review Manager (RevMan), Version 5.3 (Review Manager 2014).

Selection of studies
Fourteen review authors (CRMM, ER, FLM, HK, KBR, LA, MH, MS, NP, OJS, SJH, SR, TB and TDN) will work together in groups of two and independently screen titles and abstracts of all records retrieved by the searches; we will resolve uncertainty or disagreement by consensus. We will obtain the full-text of all potentially relevant reports and assess each against our inclusion criteria. We will discuss disagreements and will consult a third review author (OJS) if agreement cannot be reached. We will list relevant non-randomised studies that do not fulfill the inclusion criteria with reasons for exclusion in the ‘Characteristics of excluded studies’ table.

Data extraction and management
We will develop data extraction forms to facilitate standardisation of data extraction. We will extract data on participants, study design and methods, interventions, adverse events, and relevant data for ‘Risk of bias’ assessments.

All review authors will extract data. The authors will work together in groups of two and each pair will complete the data collection form independently to ensure accuracy. We will resolve disagreements by discussion or use an arbiter if required. CRMM, FLM, HK, MH, NP, and OJS will enter the data into RevMan (Review Manager 2014). In cases where there are not enough data, or where data in the published trial reports are unclear, we will contact authors requesting them to clarify the missing information.

Assessment of risk of bias in included studies
For each included study, two review authors (LA, SJH, NP or OJS) will use ACROBAT-NRSI (Sterne 2014), to independently assess the risk of bias of comparative cohort studies and case-control studies across the following seven domains.

1. Possible bias due to confounding factors
   We will assess risk of bias due to:
   - Comorbidity;
   - Age;
   - Gender;
   - Subtypes of ADHD;
   - Socioeconomic factors;
   - Switch between ADHD medications;
   - Adjustment of medication; and
   - Any other confounding factor in the study.

2. Possible bias due to selection of participants
   We will assess risk of bias due to:
   - Inclusion of patients;
   - Time from diagnosis to inclusion in study; and
   - Naive to methylphenidate versus non-naive patients.

   For case-control studies, we will assess risk of bias due to:
   - Selection of controls.

3. Possible bias due to measurement of interventions
   We will assess risk of bias due to:
   - Measurement of intervention status at start of follow-up;
   and
   - Self reporting of intervention status.

4. Possible bias due to departures from intended interventions
   We will assess risk of bias due to:
   - Compliance with assigned medication;
   - Practitioner administration;
   - Characteristics of the healthcare setting, for instance, public outpatient versus hospital outpatient;
• Adverse events; and
• Lack of efficacy of treatment.

5. Possible bias due to missing data
We will assess risk of bias due to:
• Loss to follow-up.

For case-control studies, we will assess risk of bias due to:
• Difference in follow-up between cases and controls.

6. Possible bias in measurement of outcomes
We will assess risk of bias due to:
• Self reporting of adverse events; and
• Error in instruments measuring adverse events.

7. Possible bias in selection of reported results
We will assess risk of bias due to:
• Type of analysis; and
• Selection of results.

Review authors will judge each domain to be at low risk of bias, moderate risk of bias, serious risk of bias, critical risk of bias, or no information, as follows.

Low risk of bias
Description: The study is comparable to a well-performed RCT.
Judgement: The study is judged to be at low risk of bias for all domains.

Moderate risk of bias
Description: The study is sound for a non-randomised study, but cannot be considered comparable to a well-performed RCT.
Judgement: The study is judged to be at low or moderate risk of bias for all domains.

Serious risk of bias
Description: The study has some important problems.
Judgement: The study is judged to be at serious risk of bias in at least one domain, but not at critical risk of bias in any domain.

Critical risk of bias
Description: The study is too problematic to provide any useful evidence on the effects of the intervention.
Judgement: The study is judged to be at critical risk of bias in at least one domain.

No information
Description: There is no information on which to base a judgment about risk of bias.
Judgement: There is no clear indication that the study is at serious or critical risk of bias and there is lack of information in one or more key domains of bias.
Review authors will resolve any disagreements by discussion and will report any discussions on the data extraction forms.

Measures of treatment effect

Dichotomous data
We will summarise dichotomous data as risk ratios (RR) with 95% confidence intervals (CI). We will calculate the risk difference (RD) and the number needed to treat for an additional harmful outcome (NNTH). We will present pooled prevalence data from non-comparative studies.

Continuous data
For continuous data, we will calculate the mean difference (MD) between the two groups and present it with 95% CI. We will use the overall MD, where possible, to compare outcome measures from trials. We will estimate the standardised MD (SMD) where studies use different measures to assess the same outcome. If trials do not report means and standard deviation (SDs) but report other values, such as t-tests and P values, we will calculate the SD using the methods described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

Dealing with missing data
We will try to obtain missing data by contacting the authors of the studies. If data remain unavailable, we will try to estimate the missing data using the available information. (If the SD is missing we will estimate it from a standard error if reported). We will also attempt to impute missing SDs for continuous data from another study that has similar summary statistics. We will evaluate the methods used to handle the missing data by excluding these studies in a sensitivity analysis, and we will discuss the extent to which the missing data are likely to influence the results of the study.

Assessment of heterogeneity
We will assess the following types of heterogeneity: clinical (variability in participants, interventions or setting); methodological (variation in study designs); and statistical heterogeneity (variation in intervention effects). Heterogeneity between studies will be assessed by visual inspection of the forest plot for overlapping CI; using the Chi² test for homogeneity with a significance level of α (alpha) = 0.1, and the I² statistic for quantifying inconsistency (estimating the percentage of variation in effect estimates due to
heterogeneity rather than sampling error), where \(I^2\) values between 0% and 40% will be judged to indicate little heterogeneity, between 30% and 60% to indicate moderate heterogeneity, between 50% and 90% to indicate substantial heterogeneity, and between 75% and 100% to indicate considerable heterogeneity (Higgins 2011). We will abstain from conducting a meta-analysis if there is a very high level of heterogeneity and the trials seem to address different questions. If it is not possible to conduct a meta-analysis we will provide a narrative description of the pooled prevalence estimate.

Study characteristics that may be important to assess include the following:
1. Number of confounders included in the models; and
2. Analysis technique used.

Assessment of reporting biases

Reporting bias and missing studies are a more complex issue for non-randomised studies than for RCTs. Registration and publication of protocols for non-randomised studies is not as common as for RCTs. We aim to include a wide range of studies by using a broad search strategy, and we will handle different forms of reporting bias, especially publication bias and outcome reporting bias, according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will draw funnel plots (estimated differences in treatment effects against their standard error) and perform Egger’s statistical test for small-study effects (Egger 1997). We will not visually inspect the funnel plot if there are less than 10 studies in the meta-analysis, as recommended in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Asymmetry could be due to publication bias, but could also be due to genuine heterogeneity between small and large trials (Higgins 2011).

Data synthesis

We will include the following comparisons.

1. Comparative studies
   - Case-control studies: intervention group compared to placebo or no intervention,
   - Cohort studies: intervention group compared to baseline values of the intervention group.

2. Non-comparative studies
   - We will only use case studies to identify less common (rare) adverse events as defined according to the brand leader’s Summary of Product Characteristics (SPC; Aagaard 2009).
   - We will divide non-comparative cohort studies into subgroups (for example, nervous system, digestive organ system), and will report the different harms under each subgroup.

We are aware that some studies could have combined designs (for example, cohort and case-control study design). We will assess these separately. Furthermore, we will include studies that compare co-interventions, providing the compared intervention groups receive the same co-interventions.

Our analysis and conclusions of the results will differ between comparative and non-comparative studies. We will use comparative studies, such as case-control studies and comparative cohort studies, to evaluate the RR of harms. For the comparative studies we will perform a meta-analysis according to recommendations in the latest version of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will also conduct ‘Risk of bias’ assessments by using ACROBAT-NRSI (Sterne 2014).

Assuming clinical heterogeneity is not excessive (for example, there is not too much variability in participants’ characteristics), we will perform a meta-analysis of the results using the generic inverse variance method. This method gives more weight to larger studies, thus reducing imprecision in the pooled estimate of effect. We will use the random-effects model in all meta-analyses and the fixed-effect model in sensitivity analyses. We will present and analyse the pooled estimates of the different adverse events according to study design and study characteristics (for example, prospective study, retrospective study and whether or not the study has a comparison group).

Subgroup analysis and investigation of heterogeneity

When possible, we will conduct the following subgroup analyses.
1. Age (birth to 6 years, 7 to 11 years, and 12 to 18 years).
2. Sex (boys compared to girls).
3. Comorbidity (children with comorbid disorders compared to children without comorbid disorders).
4. Subtype of ADHD (predominantly inattentive type versus combined type).

Sensitivity analysis

We will assess the impact of heterogeneity on the overall pooled effect estimate by removing studies (‘outliers’) that are contributing to the heterogeneity. We will remove outliers one by one and assess the impact on the overall outcome. We will conduct sensitivity analyses to determine whether findings are sensitive to the following:
1. Decisions made during the review process such as our assessment of the level of clinical heterogeneity;
2. The impact of bias (studies with critical and serious risk of bias);
3. Analytical technique used (for example, fixed-effect and random-effects models);
4. Type of data collection (for example, different ways to measure adverse events); and
5. Imputed data (comparing the analyses with available outcome data with those following the intention-to-treat (ITT) principle).

'Summary of findings' tables
We will construct a 'Summary of findings' table for all outcomes, using the software of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group: GRADEpro GDT 2015. We will assess the quality of the body of evidence using the GRADE approach based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. Considerations are due to: within-trial risk of bias; the directness of the evidence; heterogeneity of the data; precision of effect estimates; and risk of publication bias (Andrews 2013a; Andrews 2013b; Balshem 2013; Brunetti 2013; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2013a; Guyatt 2013b; Guyatt 2013c; Mustafa 2013).

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REFERENCES

Additional references

Aagaard 2009

AAP 2011

Andrews 2013a

Andrews 2013b

APA 1980

APA 1987

APA 1994
Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents - assessment of harmful effects in non-randomised studies (Protocol)

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Czamara 2013 Czamara D, Tiesler CM, Kohlböck G, Berdel D, Hoffmann B, Bauer CP, et al. Children with ADHD symptoms have a

Dalsgaard 2015a


Dalsgaard 2015b


Donnelly 2004


Egger 1997


Elgen 2015


Engert 2008


Evans 2001


GRADEpro GDT 2015 [Computer program]


Greenhill 2006


Guyatt 2011a


Guyatt 2011b


Guyatt 2011c


Guyatt 2011d


Guyatt 2011e


Guyatt 2011f


Guyatt 2011g


Guyatt 2013a


Guyatt 2013b

Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents - assessment of harmful effects in non-randomised studies (Protocol)

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Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents: assessment of harmful effects in non-randomised studies (Protocol)

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MTA 1999

Mustafa 2013

NCCMH 2009a

NCCMH 2009b

Newcorn 2008

Nigg 2005

Obel 2015

Pasini 2007

Pliszka 2007

Polanczyk 2007

Polanczyk 2014

Review Manager 2014 [Computer program]

Rosa-Neto 2005

Scahill 2000

Schachar 1997

Schmidt 2009

Schulz 2012

Schweitzer 2004
Sergeant 2003

Shaw 2012

Solanto 1998

Sonuga-Barke 2007

Sterne 2014

Stevenson 1989

Stoebbe 2015

Swanson 2004

Swanson 2009

Taylor 2004

U.S. FDA 2011

Van Lieshout 2015

Volkow 1998

Volkow 2004

Volkow 2012

WHO 1977

WHO 1992

Willcut 2012

Yang 2004
Yoshimasu 2012

* Indicates the major publication for the study

## Additional Tables

### Table 1. Study design

<table>
<thead>
<tr>
<th>Study design</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort study</td>
<td>An observational study in which a defined group of people (the cohort) is followed over time. The outcomes of people in subsets of this cohort are compared, to examine people who were exposed or not exposed (or exposed at different levels) to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective (or historical) cohort study identifies subjects from past records and follows them from the time of those records to the present. Because subjects are not allocated by the investigator to different interventions or other exposures, adjusted analysis is usually required to minimise the influence of other factors (confounders)</td>
</tr>
<tr>
<td>Case-control study</td>
<td>A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls), and which seeks to find associations between the outcome and prior exposure to particular risk factors. This design is particularly useful where the outcome is rare and past exposure can be reliably measured. Case-control studies are usually retrospective, but not always</td>
</tr>
</tbody>
</table>

Taken from the Cochrane Glossary.
## Appendix 1. Search strategies

<table>
<thead>
<tr>
<th>Database</th>
<th>Search strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovid MEDLINE</td>
<td><strong>Efficacy</strong></td>
</tr>
<tr>
<td></td>
<td>1. exp &quot;attention deficit and disruptive behavior disorders&quot;/</td>
</tr>
<tr>
<td></td>
<td>2. adhd.mp.</td>
</tr>
<tr>
<td></td>
<td>3. addh.mp.</td>
</tr>
<tr>
<td></td>
<td>4. adhs.mp.</td>
</tr>
<tr>
<td></td>
<td>5. (ad adj hd).mp.</td>
</tr>
<tr>
<td></td>
<td>6. ((attention* or behav*) adj3 (defic* or dysfunc* or disorder*)).mp.</td>
</tr>
<tr>
<td></td>
<td>7. ((disrupt* adj3 disorder*) or (disrupt* adj3 behav*) or (defian* adj3 disorder*) or (defian* adj3 behav*)).mp.</td>
</tr>
<tr>
<td></td>
<td>8. (impulsiv* or inattentiv* or inattention*).mp.</td>
</tr>
<tr>
<td></td>
<td>9. hyperactiv*.mp.</td>
</tr>
<tr>
<td></td>
<td>10. hyperkinesis*.mp.</td>
</tr>
<tr>
<td></td>
<td>11. exp Hyperkinesis/</td>
</tr>
<tr>
<td></td>
<td>12. (minimal adj brain adj3 disorder*).mp.</td>
</tr>
<tr>
<td></td>
<td>13. (minimal adj brain adj3 dysfunction*).mp.</td>
</tr>
<tr>
<td></td>
<td>14. (minimal adj brain adj3 damage*).mp.</td>
</tr>
<tr>
<td></td>
<td>15. or/1-14</td>
</tr>
<tr>
<td></td>
<td>16. randomized controlled trial.pt.</td>
</tr>
<tr>
<td></td>
<td>17. controlled clinical trial.pt.</td>
</tr>
<tr>
<td></td>
<td>18. randomized controlled trials.mp.</td>
</tr>
<tr>
<td></td>
<td>19. random allocation.mp.</td>
</tr>
<tr>
<td></td>
<td>20. double blind method.mp.</td>
</tr>
<tr>
<td></td>
<td>21. single blind method.mp.</td>
</tr>
<tr>
<td></td>
<td>22. clinical trial.pt.</td>
</tr>
<tr>
<td></td>
<td>23. (clin* adj25 trial*).ti,ab.</td>
</tr>
<tr>
<td></td>
<td>24. ((singl* or doubl* or tripl* or trebl*) adj25 (blind* or mask* or dummy*)).mp.</td>
</tr>
<tr>
<td></td>
<td>25. exp Clinical Trial/</td>
</tr>
<tr>
<td></td>
<td>26. placebos.mp.</td>
</tr>
<tr>
<td></td>
<td>27. placebo*.ti,ab.</td>
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<tr>
<td></td>
<td>28. random*.ti,ab.</td>
</tr>
<tr>
<td></td>
<td>29. comparative study.mp.</td>
</tr>
<tr>
<td></td>
<td>30. Evaluation Studies as Topic/</td>
</tr>
<tr>
<td></td>
<td>31. exp Clinical Trials as Topic/</td>
</tr>
<tr>
<td></td>
<td>32. follow up studies.mp.</td>
</tr>
<tr>
<td></td>
<td>33. prospective studies.mp.</td>
</tr>
<tr>
<td></td>
<td>34. (control* or prospectiv* or volunteer*).ti,ab.</td>
</tr>
<tr>
<td></td>
<td>35. Epidemiologic studies/</td>
</tr>
<tr>
<td></td>
<td>36. Exp case control studies/</td>
</tr>
<tr>
<td></td>
<td>37. Exp cohort studies/</td>
</tr>
<tr>
<td></td>
<td>38. Case control.tw.</td>
</tr>
<tr>
<td></td>
<td>39. (cohort adj (study or studies)).tw.</td>
</tr>
<tr>
<td></td>
<td>40. Cohort analy$.tw.</td>
</tr>
<tr>
<td></td>
<td>41. (Follow up adj (study or studies)).tw.</td>
</tr>
</tbody>
</table>
42. (observational adj (study or studies)).tw.
43. Longitudinal.tw.
44. Retrospective.tw.
45. Cross sectional.tw.
46. Cross-sectional studies
47. or/16-46
48. 15 and 47
49. Methylphenidate.mp. or Methylphenidate/
50. Aptsesio.mp.
51. Attenta.mp.
52. Biphenitin.mp.
53. Calocain.mp.
54. Centedrin*.mp.
55. Concerta.mp.
56. Daytrana.mp.
57. Dexamethylphenidat*.mp.
58. Difumenil.mp.
59. Elmifiten.mp.
60. Equasymp.m.
61. Focalin.mp.
62. Matoride.mp.
63. Medikid.mp.
64. Medikinet.mp.
65. Meridil.mp.
66. Metadata.mp.
67. Methyl phenidat*.mp.
68. Methyl phenidylacetat*.mp.
69. Methylfenid*.mp.
70. Methylin.mp.
71. Methylfenidan.mp.
72. Methylphenid*.mp.
73. Methyl phenidyl acetat*.mp.
74. Methyppatch.mp.
75. Metidate.mp.
76. Metilfenidato.mp.
77. Motiron.mp.
78. MPH.mp.
79. Omozin.mp.
80. Penid.mp.
81. Phenidyl hydrochlorid*.mp.
82. Phenidylat*.mp.
83. Plimasin*.mp.
84. PMS-Methylphenid*.mp.
85. Quazym.mp/
86. Quilli*.mp.
87. Richter Works.mp.
88. Riphenidat*.mp.
89. Ritalin*.mp.
| 90. | Rubifen.mp. |
| 91. | Stimdat*.mp. |
| 92. | Tifinidat.mp. |
| 93. | Tranquilyn.mp. |
| 94. | Tsentedrin*.mp. |
| 95. | or/49-94 |
| 96. | 48 and 95 |
| 97. | exp Child/ |
| 98. | exp Adolescent/ |
| 99. | exp Infant/ |
| 100. | (child* or boy* or girl* or adolescen* or teen* or preschool or pre school or infant* or baby or babies or toddler* or school child* or youth*).mp. |
| 101. | or/97-100 |
| 102. | 96 and 101 |

### Adverse events

1. Methylphenidate.mp. or Methylphenidate/
2. Aptensio.mp.
3. Attenta.mp.
4. Biphentin.mp.
5. Calocain.mp.
7. Concerta.mp.
8. Daytrana.mp.
10. Difumenil.mp.
11. Elmifiten.mp.
12. Equasym.mp.
13. Focalin.mp.
15. Medikid.mp.
17. Meridil.mp.
18. Metadate.mp.
22. Methylin.mp.
23. Methylofenidan.mp.
25. Methyl phenidyl acetat*.mp.
26. Methypatch.mp.
27. Metidate.mp.
28. Metilfenidato.mp.
29. Motiron.mp.
30. MPH.mp.
31. Omozin.mp.
32. Penid.mp.
33. Phenidyl hydrochlorid*.mp.
34. Phenidylat.mp.
35. Plimasin.mp.
36. PMS-Methylphenid*.mp.
37. Quazym.mp.
38. Quilli.mp.
40. Riphenidat.mp.
41. Ritalin*.mp.
42. Rubifen.mp.
43. Stimdat.mp.
44. Tifinidat.mp.
45. Tranquilyn.mp.
46. Tsentedrin.mp.
47. or/1-46
48. (ae or co or de).fs.
49. (safe or safety or (side adj1 effect*) or (undesirable adj1 effect*) or (treatment adj1 emergent) or tolerability or tolerance or tolerate or toxicity or toxic or adr or ad or harm or harms or harmful or complication* or risk or risks or (unintended adj1 event*) or (unintended adj1 effect*)).ti,ab.
50. (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.
51. or/48-50
52. exp Child/
53. exp Adolescent/
54. exp Infant/
55. (child* or boy* or girl* or adolescence* or teen* or preschool or pre school or infant* or baby or babies or toddler* or school child* or youth*).mp.
56. or/52-55
57. exp Mood Disorders/
58. (depression or depressive).ti,ab.
59. exp Psychotic Disorders/
60. (psychosis or (psychotic adj4 symptom*)).ti,ab.
61. exp Body Weight/ or Anorexia/
62. ((loss or lose or losing or reduc*) adj3 (weight or appetite)).ti,ab.
63. ((reduc* or retard* or inhibit* or deficit*) adj4 growth).ti,ab.
64. exp Hypertension/
65. Heart Rate/
66. exp tachycardia/
67. (increas* adj4 (heart rate or pulse or blood pressure)).ti,ab.
68. exp Death, Sudden/
69. death.ti,ab.
70. exp Infertility/
71. ((loss or reduc*) adj4 fertility) or infertility).ti,ab.
72. exp Carcinogens/
73. exp Neoplasms/
74. ((risk adj2 cancer) or (cytogenetic adj2 effect*)).ti,ab.
75. or/57-74
76. 51 or 75
77. 47 and 56 and 76
78. Methylphenidate/ae, po, to
**CONTRIBUTIONS OF AUTHORS**

All of the authors contributed to writing this protocol.

KBR developed the search strategy.

OJS, NP, ER, HBK, CRMM, FLM, MH, TDN, MS, SR, KBR, SJH, LA and TB will perform the selection of the studies.

All authors will contribute to data extraction and evaluation of bias.

OJS, NP, ER, HBK, CRMM, and FLM will enter data into RevMan.

OJS, NP, ER, HBK, RK, SJH, and LA will perform the statistical analysis.

All authors will contribute to writing the discussion and the final review.

**DECLARATIONS OF INTEREST**

Ole Jakob Storebø - none known.

Nadia Pedersen - none known.

Erica Ramstad - none known.

Helle B. Krogh - none known.

Carlos R Moreira-Maia - receives financial research support from the government agencies: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq); has served as a speaker to Novartis, and developed educational material for Novartis and Libbs; received travel awards from the Health Technology Assessment Institute (IATS), Universidade Federal do Rio Grande do Sul (UFRGS); and travel, accommodation and registration support to the fourth and fifth World Congress on ADHD from the World Federation of ADHD. Carlos is author on Maia 2008 and Maia 2014 and declares that he will not take part in extracting data from the study, or in conducting the meta-analysis.

Frederik L Magnusson - none known.

Mathilde Holmskov - none known.

Trine Danvad Nilausen - none known.

Maria Skoog - none known.

Susanne Rosendal - none known.

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Donna Gillies - none known.

Kirsten Buch Rasmussen - none known.

Dorothy Gauci - none known.

Morris Zwi - sits on the Paediatric Medicines Expert Advisory Group at the Medicines and Healthcare Regulatory Agency, which considers applications regarding the licensing of paediatric medicines. Payment for MZ’s attendance at this meeting goes to his National Health Service (NHS) organisation.
Richard Kirubakaran - is currently employed by the Cochrane South Asia, salary funded by Effective Healthcare Research Consortium (EHCRC) for the Department for International Development (DFID), UK.

Bente Forsbøl - none known.

Sasja J Håkonsen - none known.

Lise Aagaard - has received travelling grants from pharmaceutical companies Pfizer, Swedish Orphan BioVitrum and Shire, none of which were related to this review.

Erik Simonsen - none known.

Christian Gluud - none known.

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- Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital, Denmark.
  Maria Skoog and Christian Gluud worked on this protocol during office hours

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