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

assessment of harmful effects in non-randomised studies

Storebø, Ole Jakob; Pedersen, Nadia ; Ramstad, Erica; Krogh, Helle B.; Moreira-Maia, Carlos R; Magnusson, Frederik L; Holmskov, Mathilde ; Danvad Nilausen, Trine ; Skoog, Maria ; Rosendal, Susanne ; Groth, Camilla; Gillies, Donna ; Buch Rasmussen, Kirsten; Gauci, Dorothy; Zwi, Morris; Kirubakaran, Richard; Forsbøl, Bente ; Juul Håkonsen, Sasja; Aagaard, Lise; Simonsen, Erik; Gluud, Christian

Published in:
Cochrane Database of Systematic Reviews

DOI:
10.1002/14651858.CD012069

Publication date:
2016

Document version
Publisher's PDF, also known as Version of record

Document license
CC BY-NC-SA

Citation for pulished version (APA):
Storebø, O. J., Pedersen, N., Ramstad, E., Krogh, H. B., Moreira-Maia, C. R., Magnusson, F. L., ... Gluud, C. (2016). Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents: assessment of harmful effects in non-randomised studies. Cochrane Database of Systematic Reviews, 2016(2), [CD012069]. https://doi.org/10.1002/14651858.CD012069

Cochrane Library

Cochrane Database of Systematic Reviews

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

Storebø OJ, Pedersen N, Ramstad E, Krogh HB, Moreira-Maia CR, Magnusson FL, Holmskov M, Nilausen TD, Skoog M, Rosendal S, Groth C, Gillies D, Buch Rasmussen K, Gauci D, Zwi M, Kirubakaran R, Forsbøl B, Håkonsen SJ, Aagaard L, Simonsen E, Gluud C

Storebø OJ, Pedersen N, Ramstad E, Krogh HB, Moreira-Maia CR, Magnusson FL, Holmskov M, Nilausen TD, Skoog M, Rosendal S, Groth C, Gillies D, Buch Rasmussen K, Gauci D, Zwi M, Kirubakaran R, Forsbøl B, Håkonsen SJ, Aagaard L, Simonsen E, Gluud C.
Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents - assessment of harmful effects in non-randomised studies.
Cochrane Database of Systematic Reviews 2016, Issue 2. Art. No.: CD012069.
DOI: 10.1002/14651858.CD012069.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

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

Ole Jakob Storebø[1,2,3], Nadia Pedersen[2], Erica Ramstad[1,2], Helle B. Krogh[1,2], Carlos R Moreira-Maia[4], Frederik L Magnusson[2], Mathilde Holmskov[2], Trine Danvad Nilausen[2], Maria Skoog[5], Susanne Rosendal[6], Camilla Groth[7], Donna Gillies[8], Kirsten Buch Rasmussen[2], Dorothy Gauci[9], Morris Zwi[10], Richard Kirubakaran[11], Bente Forsbøl[12], Sasja J Håkonsen[13], Lise Aagaard[14], Erik Simonsen[2], Christian Gluud[5,15]

[1]Child and Adolescent Psychiatric Department, Region Zealand, Roskilde, Denmark. [2]Psychiatric Research Unit, Region Zealand Psychiatry, Slagelse, Denmark. [3]Department of Psychology, Faculty of Health Science, University of Southern Denmark, Odense, Denmark. [4]Department of Psychiatry, Federal University of Rio Grande do Sul, Porto Alegre, Brazil. [5]Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital, Copenhagen, Denmark. [6]Psychiatric Centre North Zealand, The Capital Region of Denmark, Denmark. [7]Pediatric Department, Herlev University Hospital, Herlev, Denmark. [8]Western Sydney Local Health District - Mental Health, Parramatta, Australia. [9]Directorate for Health Information and Research, Department of Health, G'Mangia, Malta. [10]Islington Child and Adolescent Mental Health Service, Whittington Health, London, UK. [11]South Asian Cochrane Network & Center, Prof. BV Moses Center for Evidence-Informed Health Care and Health Policy, Christian Medical College, Vellore, India. [12]Child and Adolescent Psychiatric Clinic, Region Sjælland, Holbæk, Denmark. [13]Department of Health Science and Technology, Aalborg University, Aalborg, Denmark. [14]Faculty of Health Sciences, Department of Public Health, University of Southern Denmark, Odense, Denmark. [15]The Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 7812, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Contact address: Ole Jakob Storebø, Child and Adolescent Psychiatric Department, Region Zealand, Birkevaenget 3, Roskilde, 4300, Denmark. ojst@regionsjaelland.dk.

Editorial group: Cochrane Developmental, Psychosocial and Learning Problems Group.
Publication status and date: New, published in Issue 2, 2016.

Citation: Storebø OJ, Pedersen N, Ramstad E, Krogh HB, Moreira-Maia CR, Magnusson FL, Holmskov M, Nilausen TD, Skoog M, Rosendal S, Groth C, Gillies D, Buch Rasmussen K, Gauci D, Zwi M, Kirubakaran R, Forsbøl B, Håkonsen SJ, Aagaard L, Simonsen E, Gluud C. Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents - assessment of harmful effects in non-randomised studies. *Cochrane Database of Systematic Reviews* 2016, Issue 2. Art. No.: CD012069. DOI: 10.1002/14651858.CD012069.

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 inattention, 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, Schweitzer 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 non-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:

1. A diagnosis of ADHD made according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) Third Edition (DSM-III; APA 1980), Third Edition Revised (DSM-III-R; APA 1987), Fourth Edition (DSM-IV; APA 1994), and Fifth Edition (DSM-5; APA 2013).
2. A diagnosis of hyperkinetic disorders made in accordance with the International Classification of Diseases (ICD) Ninth (ICD-9; WHO 1977) and Tenth (ICD-10; WHO 1992) Revisions.

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 fulfil 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 I^2 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 2011; Brunetti 2013; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2013a; Guyatt 2013b; Guyatt 2013c; Mustafa 2013).

ACKNOWLEDGEMENTS

We thank Janus Christian Jacobsen, Ph.D., at the Copenhagen Trial Unit, for elaborating the idea for this review.

We thank Trine Lacoppidan Kæstel, Research Librarian, at the Psychiatric Research Unit, Region Zealand, Denmark, for helping with searches and descriptions of measurement scales.

We thank Jesper Pedersen, Ph.D., M.D., at the Department of Children and Youth Psychiatry, Region Zealand, Denmark, for supporting this project.

We thank Per Hove Thomsen, Ph.D., M.D., Department of Clinical Medicine - Psychiatric Hospital for Children and Adolescents, Aarhus University.

We thank Jacob Riis, User Experience Lead, and Rasmus Moustgaard, Senior Systems Architect, at the Nordic Cochrane Centre, Copenhagen, Denmark, for helping with Review Manager issues.

Thanks also to the Psychiatric Research Unit, Region Zealand Psychiatry, Roskilde, Denmark; Region Zealand Research Foundation, Denmark; and the Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital, Copenhagen, Denmark, for funding and enabling the review.

We thank Julian Higgins, Professor of Evidence Synthesis at the University of Bristol, for his advice on the *ACROBAT-NRSI* for assessing the risk of bias in non-randomised studies.

We also warmly thank Geraldine McDonald (Co-ordinating Editor), Joanne Wilson (Managing Editor), Gemma O'Loughlin (Assistant Managing Editor) and Margaret Anderson (Trials Search Co-ordinator) of the Cochrane Developmental, Psychosocial and Learning Problems Group for providing help and support.

Finally, we are grateful for the advice and support received from Toby Lasserson (Senior Editor), and David Tovey (Editor-in-Chief) of the Cochrane Collaboration.

REFERENCES

Additional references

Aagaard 2009
Aagaard L, Hansen EH. Information about ADRs explored by pharmacovigilance approaches: a qualitative review of studies on antibiotics, SSRIs and NSAIDs. *BMC Clinical Pharmacology* 2009;**9**:4. [DOI: 10.1186/1472-6904-9-4]

AAP 2011
American Academy of Pediatrics Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management. ADHD: clinical practice guideline for the diagnosis, evaluation, and the treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics* 2011;**128**(5):1077–22.

Andrews 2013a
Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *Journal of Clinical Epidemiology* 2013;**66**(7):719-25. [DOI: 10.1016/j.jclinepi.2012.03.013]

Andrews 2013b
Andrews JC, Schünemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation - determinants of a recommendation's direction and strength. *Journal of Clinical Epidemiology* 2013;**66**(7):726-35. [DOI: 10.1016/j.jclinepi.2013.02.003]

APA 1980
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-III)*. 3rd Edition. Washington, DC: American Psychiatric Association, 1980.

APA 1987
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM III-R)*. 3rd Edition. Washington, DC: American Psychiatric Association, 1987.

APA 1994
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. 4th Edition.

Washington, DC: American Psychiatric Association, 1994.

APA 2000
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: Text revision (DSM-IV-TR)*. 4th Edition. Washington, DC: American Psychiatric Association, 2000.

APA 2013
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. 5th Edition. Washington, DC: American Psychiatric Association, 2013.

Balshem 2011
Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology* 2011; **64**(4):401-6. [DOI: 10.1016/j.jclinepi.2010.07.015]

Barkley 1977
Barkley RA. A review of stimulant drug research with hyperactive children. *Journal of Child Psychology and Psychiatry* 1977;**18**(2):137–65. [DOI: 10.1111/j.1469-7610.1977.tb00425.x]

Barkley 1981
Barkley RA. The use of psychopharmacology to study reciprocal influences in parent-child interaction. *Journal of Abnormal Child Psychology* 1981;**9**(3):303–10. [PUBMED: 7320347]

Barkley 1989
Barkley RA. Hyperactive girls and boys: stimulant drug effects on mother-child interactions. *Journal of Child Psychology and Psychiatry* 1989;**30**(3):379–90. [DOI: 10.1111/j.1469-7610.1989.tb00253.x]

Barkley 1991
Barkley RA, DuPaul GJ, McMurray MB. Attention deficit disorder with and without hyperactivity: clinical response to three dose levels of methylphenidate. *Pediatrics* 1991;**87** (4):519–31. [PUBMED: 2011430]

Bhutta 2002
Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. *JAMA* 2002;**288**(6):728–37. [PUBMED: 12169077]

Biederman 2003
Biederman J. Pharmacotherapy for attention-deficit/hyperactivity disorder (ADHD) decreases the risk for substance abuse: findings from a longitudinal follow-up of youths with and without ADHD. *Journal of Clinical Psychiatry* 2003;**64**(Suppl 11):3–8. [PUBMED: 14529323]

Bolea-Alamañac 2014
Bolea-Alamañac B, Nutt DJ, Adamou M, Asherson P, Bazire S, Coghill D, et al. Evidence-based guidelines for the pharmacological management of attention deficit hyperactivity disorder: update on recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacoly* 2014;**28**(3):179–203.

Brunetti 2013
Brunetti M, Shemilt I, Pregno S, Vale L, Oxman AD, Lord J, et al. GRADE guidelines: 10. Considering resource use and rating the quality of economic evidence. *Journal of Clinical Epidemiology* 2013;**66**(2):140-50. [DOI: 10.1016/j.jclinepi.2012.04.012]

Burnett 2014
Burnett A, Davey CG, Wood SJ, Wilson-Ching M, Molloy C, Cheong JLY, et al. Extremely preterm birth and adolescent mental health in a geographical cohort born in the 1990s. *Psychological Medicine* 2014;**44**(7):1533–44. [DOI: 10.1017/S0033291713002158]

Castellanos 2006
Castellanos FX, Sonuga-Barke EJS, Milham MP, Tannock R. Characterizing cognition in ADHD: beyond executive dysfunction. *Trends in Cognitive Sciences* 2006;**10**(3): 117–23. [DOI: 10.1016/j.tics.2006.01.011]

Catalá-López 2013
Catalá-López F, Ridao M, Sanfélix-Gimenob G, Peiró S. Cost-effectiveness of pharmacological treatment of attention deficit hyperactivity disorder in children and adolescents: qualitative synthesis of scientific evidence [Coste–efectividad del tratamiento farmacológico del trastorno por déficit de atención e hiperactividad en niños y adolescentes: síntesis cualitativa de la evidencia científica]. *Revista de Psiquiatría y Salud Mental* 2013;**6**(4):168–77. [DOI: 10.1016/j.rpsm.2012.12.002]

CDC 2015
Centers for Disease Control and Prevention (CDC). QuickStats: percentage* of children aged 5-17 years with diagnosed attention deficit/hyperactivity disorder (ADHD), † by Poverty Status§ and Sex - National Health Interview Survey,¶ 2011-2014. *Morbidity and Mortality Weekly Report* 2015;**64**(40):1156. [PUBMED: 26469562]

Connor 2002
Connor DF. Preschool attention deficit hyperactivity disorder: a review of prevalence, diagnosis, neurobiology, and stimulant treatment. *Journal of Developmental and Behavioral Pediatrics* 2002;**23**(Suppl 1):S1–9. [PUBMED: 11875284]

Cortese 2016
Cortese S, Moreira-Maia CR, St. Fleur D, Morcillo-Peñalver C, Rohde LA, Faraone SV. Association between ADHD and obesity: a systematic review and meta-analysis. *American Journal of Psychiatry* 2016;**173**(1):34–43. [DOI: 10.1176/appi.ajp.2015.15020266]

Cox 2004
Cox DJ, Merkel RL, Penberthy JK, Kovatchev B, Hankin CS. Impact of methylphenidate delivery profiles on driving performance of adolescents with attention-deficit/hyperactivity disorder: a pilot study. *Journal of the American Academy of Child and Adolescent Psychiatry* 2004;**43**(3): 269–75. [PUBMED: 15076259]

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

higher risk for reading, spelling and math difficulties in the GINIplus and LISAplus cohort studies. *PLoS One* 2013;**8** (5):e63859. [DOI: 10.1371/journal.pone.0063859]

Dalsgaard 2015a
Dalsgaard S, Leckman JF, Mortensen PB, Nielsen HS, Simonsen M. Effect of drugs on the risk of injuries in children with attention deficit hyperactivity disorder: a prospective cohort study. *Lancet Psychiatry* 2015;**2**(8): 702–9. [DOI: 10.1016/S2215-0366(15)00271-0]

Dalsgaard 2015b
Dalsgaard S, Østergaard SD, Leckman JF, Mortensen PB, Pedersen MG. Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study. *Lancet* 2015;**385**(9983):2190–6. [DOI: 10.1016/S0140-6736(14)61684-6]

Donnelly 2004
Donnelly M, Haby MM, Carter R, Andrews G, Vos T. Cost-effectiveness of dexamphetamine and methylphenidate for the treatment of childhood attention deficit hyperactivity disorder. *Australian and New Zealand Journal of Psychiatry* 2004;**38**(8):592–601. [PUBMED: 15298581]

Egger 1997
Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629–34. [PUBMED: 9310563]

Elgen 2015
Elgen SK, Sommerfelt K, Leversen KT, Markestad T. Minor neurodevelopmental impairments are associated with increased occurrence of ADHD symptoms in children born extremely preterm. *European Child and Adolescent Psychiatry* 2015;**24**(4):463–70. [DOI: 1007/s00787-014-0597-9]

Engert 2008
Engert V, Pruessner JC. Dopaminergic and noradrenergic contributions to functionality in ADHD: the role of methylphenidate. *Current Neuropharmacology* 2008;**6**(4): 322–8. [DOI: 10.2174/157015908787386069]

Evans 2001
Evans SW, Pelham WE, Smith BH, Bukstein O, Gnagy EM, Greiner AR, et al. Dose-response effects of methylphenidate on ecologically valid measures of academic performance and classroom behavior in adolescents with ADHD. *Experimental and Clinical Psychopharmacology* 2001;**9**(2): 163–75. [PUBMED: 11518092]

GRADEpro GDT 2015 [Computer program]
McMaster University (developed by Evidence Prime, Inc.). Available from www.gradepro.org. GRADEpro GDT: GRADEpro Guideline Development Tool. McMaster University (developed by Evidence Prime, Inc.). Available from www.gradepro.org, 2015.

Greenhill 2006
Greenhill L, Kollins S, Abikoff H, McCracken J, Riddle M, Swanson J, et al. Efficacy and safety of immediate-release methylphenidate treatment for preschoolers with ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry* 2006;**45**(11):1284–93. [DOI: 10.1097/01.chi.0000235077.32661.61]

Guyatt 2011a
Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383-94. [DOI: 10.1016/j.jclinepi.2010.04.026]

Guyatt 2011b
Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *Journal of Clinical Epidemiology* 2011;**64**(4):395-400.

Guyatt 2011c
Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence- study limitations (risk of bias). *Journal of Clinical Epidemiology* 2011;**64**(4):407-15. [DOI: 10.1016/j.jclinepi.2010.07.017]

Guyatt 2011d
Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence - imprecision. *Journal of Clinical Epidemiology* 2011;**64**(12):1283-93. [DOI: 10.1016/j.jclinepi.2011.01.012]

Guyatt 2011e
Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence - inconsistency. *Journal of Clinical Epidemiology* 2011;**64**(12):1294-302. [DOI: 10.1016/j.jclinepi.2011.03.017]

Guyatt 2011f
Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence - indirectness. *Journal of Clinical Epidemiology* 2011;**64**(12):1303-10. [DOI: 10.1016/j.jclinepi.2011.04.014]

Guyatt 2011g
Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. *Journal of Clinical Epidemiology* 2011; **64**(12):1311-6. [DOI: 10.1016/j.jclinepi.2011.06.004]

Guyatt 2013a
Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. *Journal of Clinical Epidemiology* 2013;**66**(2):151-7. [DOI: 10.1016/j.jclinepi.2012.01.006]

Guyatt 2013b
Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing summary of findings tables - binary outcomes. *Journal of Clinical Epidemiology* 2013;**66**(2):158-72. [DOI: 10.1016/j.jclinepi.2012.01.012]

Guyatt 2013c

Guyatt GH, Thorlund K, Oxman AD, Walter SD, Patrick D, Furukawa TA, et al. GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles - continuous outcomes. *Journal of Clinical Epidemiology* 2013;**66**(2):173-83. [DOI: 10.1016/j.jclinepi.2012.08.001]

Heal 2006

Heal DJ, Pierce DM. Methylphenidate and its isomers: their role in the treatment of attention-deficit hyperactivity disorder using a transdermal delivery system. *CNS Drugs* 2006;**20**(9):713–38. [PUBMED: 16953648]

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hong 2009

Hong J, Dilla T, Arellano J. A modelled economic evaluation comparing atomoxetine with methylphenidate in the treatment of children with attention-deficit/hyperactivity disorder in Spain. *BMC Psychiatry* 2009;**9**:15. [DOI: 10.1186/1471-244X-9-15]

Hong 2014

Hong SB, Kim JW, Choi BS, Hong YC, Park EJ, Shin MS, et al. Blood manganese levels in relation to comorbid behavioral and emotional problems in children with attention-deficit/hyperactivity disorder. *Psychiatry Research* 2014;**220**(1-2):418–25. [PUBMED: 25064383]

Hong 2015

Hong SB, Im MH, Kim JW, Park EJ, Shin MS, Kim BN, et al. Environmental lead exposure and attention deficit/hyperactivity disorder symptom domains in a community sample of South Korean school-age children. *Environmental Health Perspectives* 2015;**123**(3):271–6. [PUBMED: 25280233]

ICH 1996

International Council for Harmonisation Expert Working Group. 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) 1996. http://bit.ly/1R6G3kG (accessed 6 May 2011).

Indredavik 2004

Indredavik MS, Vik T, Heyerdahl S, Kulseng S, Fayers P, Brubakk AM. Psychiatric symptoms and disorders in adolescents with low birth weight. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2004;**89**(5):F445–50. [DOI: 10.1136/adc.2003.038943]

Jensen 2001

Jensen PS, Hinshaw SP, Kraemer HC, Lenora N, Newcorn JH, Abikoff HB, et al. ADHD comorbidity findings from the MTA study: comparing comorbid subgroups. *Journal of the American Academy of Child and Adolescent Psychiatry* 2001;**40**(2):147–58. [DOI: 10.1097/00004583-200102000-00009]

Kadesjö 2001

Kadesjö B, Gillberg C. The comorbidity of ADHD in the general population of Swedish school-age children. *Journal of Child Psychology and Psychiatry and Allied Disciplines* 2001;**42**(4):487–92. [DOI: 10.1111/1469-7610.00742]

Kadesjö 2002

Kadesjö B. [ADHD hos barn och vuxna]. *ADHD in Children and Adults*. Stockholm: Socialstyrelsen, 2002.

Kimko 1999

Kimko HC, Cross JT, Abernethy DR. Pharmacokinetics and clinical effectiveness of methylphenidate. *Clinical Pharmacokinetics* 1999;**37**(6):457-70. [PUBMED: 10628897]

King 2006

King S, Griffin S, Hodges Z, Weatherly H, Asseburg C, Richardson G, et al. A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents. *Health Technology Assessment* 2006;**10**(23):iii-iv, xiii-146. [DOI: 10.3310/hta10230]

Kovess 2015

Kovess V, Keyes KM, Hamilton A, Pez O, Bitfoi A, Koç C, et al. Maternal smoking and offspring inattention and hyperactivity: results from a cross-national European survey. *European Child and Adolescent Psychiatry* 2015;**24**(8):919–29. [DOI: 10.1007/s00787-014-0641-9]

Larsson 2014

Larsson H, Sariaslan A, Långström N, D'Onofrio B, Lichtenstein P. Family income in early childhood and subsequent attention deficit/hyperactivity disorder: a quasi-experimental study. *Journal of Child Psychology and Psychiatry and Allied Disciplines* 2014;**55**(5):428–35. [PUBMED: 24111650]

Liberati 2009

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;**339**:b2700. [DOI: 10.1136/bmj.b2700]

Maia 2008

Maia CR, Matte BC, Ludwig T, Rohde LA. Switching from methylphenidate immediate release to MPH-SODAS™ in attention-deficit/hyperactivity disorder. *European Child and Adolescent Psychiatry* 2008;**17**(3):133–42. [DOI: 10.1007/s00787-007-0647-7]

Maia 2014

Maia CR, Cortese S, Caye A, Deakin TK, Polanczyk GV, Rohde LAP. Long-term efficacy of methylphenidate immediate-release for the treatment of childhood ADHD: a systematic review and meta-analysis. Journal of Attention Disorders 2014 December 10 [Epub ahead of print].

Moher 2015

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015

statement. *Systematic Reviews* 2015;**4**(1):1–9. [DOI: 10.1186/2046-4053-4-1]

MTA 1999

MTA Cooperation Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The MTA Cooperative Group. *Archives of General Psychiatry* 1999;**56**(12):1073–86. [DOI: 10.1001/archpsyc.56.12.1073]

Mustafa 2013

Mustafa RA, Santesso N, Brozek J, Akl EA, Walter SD, Norman G, et al. The GRADE approach is reproducible in assessing the quality of evidence of quantitative evidence syntheses. *Journal of Clinical Epidemiology* 2013;**66**(7): 736–42.e5. [DOI: 10.1016/j.jclinepi.2013.02.004]

NCCMH 2009a

National Collaborating Centre for Mental Health (NCCMH) commissioned by the National Institute for Health and Clinical Excellence. Attention deficit hyperactivity disorder: diagnosis and management of ADHD in children, young people and adults. National Clinical Practice Guideline Number 72. www.nccmh.org.uk/downloads/ADHD/CG72FullGuideline.pdf (accessed 11 December 2015).

NCCMH 2009b

National Collaborating Centre for Mental Health (NCCMH) commissioned by the National Institute for Health and Clinical Excellence. Attention deficit hyperactivity disorder: the NICE guideline on diagnosis and management of ADHD in children, young people and adults. www.nice.org.uk/guidance/cg72/evidence/adhd-full-guideline-241963165 (accessed 10 December 2015).

Newcorn 2008

Newcorn JH. Co-morbidity in adults with ADHD. *CNS Spectrums* 2008;**13 Suppl 12**:12–5. [DOI: 10.1017/S1092852900003199]

Nigg 2005

Nigg JT, Casey BJ. An integrative theory of attention-deficit/hyperactivity disorder based on the cognitive and affective neurosciences. *Development and Psychopathology* 2005;**17** (3):785–806. [DOI: 10.1017/S0954579405050376]

Obel 2015

Obel C, Zhu JL, Olsen J, Breining S, Li J, Gronborg TK, et al. The risk of attention deficit hyperactivity disorder in children exposed to maternal smoking during pregnancy - a reexamination using a sibling design. Journal of Child Psychology and Psychiatry 2015 October 28 [Epub ahead of print]. [DOI: 10.1111/jcpp.12478]

Pasini 2007

Pasini A, Paloscia C, Alessandrelli R, Porfirio MC, Curatolo P. Attention and executive functions profile in drug naive ADHD subtypes. *Brain and Development* 2007;**29**(7): 400–8. [PUBMED: 17207595]

Pliszka 2007

Pliszka S, The AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 2007;**46**(7):894–921. [PUBMED: 17581453]

Polanczyk 2007

Polanczyk G, Rohde LA. Epidemiology of attention-deficit/hyperactivity disorder across the lifespan. *Current Opinion in Psychiatry* 2007;**20**(4):386–92. [PUBMED: 17551354]

Polanczyk 2014

Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. *International Journal of Epidemiology* 2014;**43**(2):434–42. [PUBMED: 24464188]

Review Manager 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rosa-Neto 2005

Rosa-Neto P, Lou HC, Cumming P, Pryds O, Karrebaek H, Lunding J, et al. Methylphenidate-evoked changes in striatal dopamine correlate with inattention and impulsivity in adolescents with attention deficit hyperactivity disorder. *NeuroImage* 2005;**25**(3):868–76. [PUBMED: 15808987]

Scahill 2000

Scahill L, Schwab-Stone M. Epidemiology of ADHD in school-age children. *Child and Adolescent Psychiatric Clinics of North America* 2000;**9**(3):541–55. [PUBMED: 10944656]

Schachar 1997

Schachar RJ, Tannock R, Cunningham C, Corkum PV. Behavioral, situational, and temporal effects of treatment of ADHD with methylphenidate. *Journal of the American Academy of Child and Adolescent Psychiatry* 1997;**36**(6): 754–63.

Schmidt 2009

Schmidt S, Petermann F. Developmental psychopathology: attention deficit hyperactivity disorder (ADHD). *BMC Psychiatry* 2009;**9**:58. [DOI: 10.1186/1471-244X-9-58]

Schulz 2012

Schulz KP, Fan J, Bédard ACV, Clerkin SM, Ivanov I, Tang CY, et al. Common and unique therapeutic mechanisms of stimulant and nonstimulant treatments for attention-deficit/hyperactivity disorder. *Archives of General Psychiatry* 2012;**69**(9):952–61. [DOI: 10.1001/archgenpsychiatry.2011.2053]

Schweitzer 2004

Schweitzer JB, Lee DO, Hanford RB, Zink CF, Ely TD, Tagamets MA, et al. Effect of methylphenidate on executive functioning in adults with attention-deficit/hyperactivity disorder: normalization of behavior but not related brain activity. *Biological Psychiatry* 2004;**56**(8):597–606. [PUBMED: 15476690]

Sergeant 2003
Sergeant JA, Geurts H, Huijbregts S, Scheres A, Oosterlaan J. The top and the bottom of ADHD: a neuropsychological perspective. *Neuroscience and Biobehavioural Reviews* 2003; **27**(7):583–92. [PUBMED: 14624803]

Shaw 2012
Shaw M, Hodgkins P, Caci H, Young S, Kahle J, Woods AG, et al. A systematic review and analysis of long-term outcomes in attention deficit hyperactivity disorder: effects of treatment and non-treatment. *BMC Medicine* 2012;**10**: 99. [DOI: 10.1186/1741-7015-10-99]

Solanto 1998
Solanto MV. Neuropsychopharmacological mechanisms of stimulant drug action in attention-deficit hyperactivity disorder: a review and integration. *Behavioural Brain Research* 1998;**94**(1):127–52. [DOI: 10.1016/S0166-4328 (97)00175-7]

Sonuga-Barke 2007
Sonuga-Barke EJS, Coghill D, Markowitz JS, Swanson JM, Vandenberghe M, Hatch SJ. Sex differences in the response of children with ADHD to once-daily formulations of methylphenidate. *Journal of American Academy of Child and Adolescent Psychiatry* 2007;**46**(6):701–10. [DOI: 10.1097/ chi.0b013e31804659f1]

Sterne 2014
Sterne JAC, Higgins JPT, Reeves BC, on behalf of the development group for ACROBAT-NRSI. A Cochrane Risk Of Bias Assessment Tool: for Non-Randomised Studies of Interventions (ACROBAT-NRSI), Version 1.0.0, 24 September 2014. Available from http://www.riskofbias.info (accessed 25 May 2015).

Stevenson 1989
Stevenson RD, Wolraich ML. Stimulant medication therapy in the treatment of children with attention deficit hyperactivity disorder. *Pediatric Clinics of North America* 1989;**36**(5):1183–97. [PUBMED: 2677938]

Storebø 2015
Storebø OJ, Ramstad E, Krogh HB, Nilausen TD, Skoog M, Holmskov M, et al. Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). *Cochrane Database of Systematic Reviews* 2015, Issue 11. [DOI: 10.1002/14651858.CD009885.pub2]

Swanson 2004
Swanson JM, Wigal SB, Wigal T, Sonuga-Barke E, Greenhill LL, Biederman J, et al. A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs study). *Pediatrics* 2004;**113** (3 Pt 1):e206–16. [PUBMED: 14993578]

Swanson 2009
Swanson J. The MTA follow-up into adolescence: implications for personalized treatment. The International Society for Research in Child and Adolescent Psychopathology (ISRCAP); 2009 June 19, Seattle. 2009.

Taylor 2004
Taylor E, Döpfner M, Sergeant J, Asherson P, Banaschewski T, Buitelaar J, et al. European clinical guidelines for hyperkinetic disorder-first upgrade. *European Child and Adolescent Psychiatry* 2004;**13 Suppl 1**:i7–i30.

U.S. FDA 2011
U.S. Food, Drug Administration (FDA). Communication about an ongoing safety review of stimulant medications used in children with attention-deficit/hyperactivity disorder (ADHD). http://1.usa.gov/1M5AYoq (accessed 6 May 2011).

Van Lieshout 2015
Van Lieshout RJ, Boyle MH, Saigal S, Morrison K, Schmidt LA. Mental health of extremely low birth weight survivors in their 30s. *Pediatrics* 2015;**135**(3):452–9. [PUBMED: 25667243]

Volkow 1998
Volkow ND, Wang GJ, Fowler JS, Gatley SJ, Logan J, Ding YS, et al. Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral methylphenidate. *American Journal of Psychiatry* 1998;**155**(10):1325–31. [PUBMED: 9766762]

Volkow 2004
Volkow ND, Wang GJ, Fowler JS, Telang F, Maynard L, Logan J, et al. Evidence that methylphenidate enhances the saliency of a mathematical task by increasing dopamine in the human brain. *American Journal of Psychiatry* 2004;**161** (7):1173–80. [PUBMED: 15229048]

Volkow 2012
Volkow ND, Wang GJ, Tomasi D, Kollins SH, Wigal TL, Newcorn JH, et al. Methylphenidate-elicited dopamine increases in ventral striatum are associated with long-term symptom improvement in adults with attention deficit hyperactivity disorder. *Journal of Neuroscience* 2012;**32**(3): 841–9. [PUBMED: 22262882]

WHO 1977
World Health Organization. International Classification of Diseases, Ninth Revision, Volume 1. Geneva: World Health Organization 1977.

WHO 1992
World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders. Clinical Descriptions and Diagnostic Guidelines*. Geneva: World Health Organization, 1992.

Willcut 2012
Willcutt EG. The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. *Neurotherapeutics* 2012;**9**(3):490–9. [DOI: 10.1007/ s13311-012-0135-8]

Yang 2004
Yang P, Chung LC, Chen CS, Chen CC. Rapid improvement in academic grades following methylphenidate treatment in attention-deficit hyperactivity disorder. *Psychiatry and Clinical Neurosciences* 2004;**58**(1):37–41. [PUBMED: 14678455]

Yoshimasu 2012
Yoshimasu K, Barbaresi WJ, Colligan RC, Voigt RG, Killian JM, Weaver AL, et al. Childhood ADHD is strongly associated with a broad range of psychiatric disorders: a population-based birth cohort study. *Journal of Child Psychology and Psychiatry and Allied Disciplines* 2012;**53**(10): 1036–43. [PUBMED: 22647074]

* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Study design

Study design	Description	
Cohort study	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)	
Case-control study	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	

Taken from the Cochrane Glossary.

APPENDICES

Appendix 1. Search strategies

Database	Search strategy
Ovid MEDLINE	**Efficacy** 1. exp "attention deficit and disruptive behavior disorders"/ 2. adhd.mp. 3. addh.mp. 4. adhs.mp. 5. (ad adj hd).mp. 6. ((attention* or behav*) adj3 (defic* or dysfunc* or disorder*)).mp. 7. ((disrupt* adj3 disorder*) or (disrupt* adj3 behav*) or (defian* adj3 disorder*) or (defian* adj3 behav*)).mp. 8. (impulsiv* or inattentiv* or inattention*).mp. 9. hyperactiv*.mp. 10. hyperkinesis*.mp. 11. exp Hyperkinesis/ 12. (minimal adj brain adj3 disorder*).mp. 13. (minimal adj brain adj3 dysfunction*).mp. 14. (minimal adj brain adj3 damage*).mp. 15. or/1-14 16. randomized controlled trial.pt. 17. controlled clinical trial.pt. 18. randomized controlled trials.mp. 19. random allocation.mp. 20. double blind method.mp. 21. single blind method.mp. 22. clinical trial.pt. 23. (clin* adj25 trial*).ti,ab. 24. ((singl* or doubl* or tripl* or trebl*) adj25 (blind* or mask* or dummy*)).mp. 25. exp Clinical Trial/ 26. placebos.mp. 27. placebo*.ti,ab. 28. random*.ti,ab. 29. comparative study.mp. 30. Evaluation Studies as Topic/ 31. exp Clinical Trials as Topic/ 32. follow up studies.mp. 33. prospective studies.mp. 34. (control* or prospectiv* or volunteer*).ti,ab. 35. Epidemiologic studies/ 36. Exp case control studies/ 37. Exp cohort studies/ 38. Case control.tw. 39. (cohort adj (study or studies)).tw. 40. Cohort analy$.tw. 41. (Follow up adj (study or studies)).tw.

(*Continued*)

	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. Aptensio.mp. 51. Attenta.mp. 52. Biphentin.mp. 53. Calocain.mp. 54. Centedrin*.mp. 55. Concerta.mp. 56. Daytrana.mp. 57. Dexmethylphenidat*.mp. 58. Difumenil.mp. 59. Elmifiten.mp. 60. Equasym.mp. 61. Focalin.mp. 62. Matoride.mp. 63. Medikid.mp. 64. Medikinet.mp. 65. Meridil.mp. 66. Metadate.mp. 67. Methyl phenidat*.mp. 68. Methyl phenidylacetat*.mp. 69. Methylfenid*.mp. 70. Methylin.mp. 71. Methylofenidan.mp. 72. Methylphenid*.mp. 73. Methyl phenidyl acetat*.mp. 74. Methypatch.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.

(*Continued*)

	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. 6. Centedrin*.mp. 7. Concerta.mp. 8. Daytrana.mp. 9. Dexmethylphenidat*.mp. 10. Difumenil.mp. 11. Elmifiten.mp. 12. Equasym.mp. 13. Focalin.mp. 14. Matoride.mp. 15. Medikid.mp. 16. Medikinet.mp. 17. Meridil.mp. 18. Metadate.mp. 19. Methyl phenidat*.mp. 20. Methyl phenidylacetat*.mp. 21. Methylfenid*.mp. 22. Methylin.mp. 23. Methylofenidan.mp. 24. Methylphenid*.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.

(*Continued*)

	34. Phenidylat*.mp. 35. Plimasin*.mp. 36. PMS-Methylphenid*.mp. 37. Quazym.mp. 38. Quilli*.mp. 39. Richter Works.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 adrs or adr or harm or harms or harmful or complication* or risk or risks or (unintended adj1 event*) or (unintended adj1 effect*)).ti,ab. 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 adolescen* 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

(*Continued*)

	79. 56 and 78 80. 77 or 79

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.

Camilla Groth - received funds from the Lundbeck Foundation to finance part of her Ph.D in the paediatric field on Tourette Syndrome. CG confirms that none of these funds were used to work on this review.

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.

SOURCES OF SUPPORT

Internal sources

- Psychiatric Research Unit, Region Zealand Psychiatry, Roskilde, Denmark.

Ole Jakob Storebø, Nadia Pedersen, Erica Ramstad, Helle B. Krogh, Frederik Løgstrup Magnusson, Mathilde Holmskov, Trine Danvad Nilausen, and Erik Simonsen worked on this protocol during office hours

- Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital, Denmark.

Maria Skoog and Christian Gluud worked on this protocol during office hours

External sources

- Region Zealand Research Foundation, Denmark, Other.

This Cochrane review is supported by a grant (DKR 532,901) from the Region Zealand Research Foundation