UNIVERSITY OF COPENHAGEN

FACULTY OF HEALTH AND MEDICAL SCIENCES

Doctoral dissertation

What are the benefits and harms of methylphenidate treatment in children and adolescents with attention deficit hyperactivity disorder?

Ole Jakob Storebø

The Faculty of Health and Medical Sciences at the University of Copenhagen has accepted this dissertation for public defence for the doctoral degree in medicine.

Copenhagen, 14. July 2022.

Bente Merete Stallknecht, Head of Faculty

The defence will take place on Wednesday 30th of November 2022, at 2.30 pm in "auditoriet", psykiatrisygehuset i Slagelse, bygning 3, stuen, Fælledvej 6, 4200 Slagelse

Officially appointed opponents:

- Professor Andre Sourander, Turku University, 1st opponent
- Professor Robin Christensen, University of Southern Denmark, 2nd opponent
- Professor Anne Katrine Pagsberg, University of Copenhagen (chair)

Leader of the defence

Professor Anne Amalie Elgaard Thorup, University of Copenhagen

Contents

Preface

The work included in this doctoral dissertation was conducted during my position as a PhD student from 2009 to 2011, at the Child and Adolescent Psychiatric Department in Region Zealand and from 2011 to 2019 during my position as senior researcher at Psychiatric Research Unit in Region Zealand. I am very grateful for the support that I have received through the years from Professor Erik Simonsen. He was the main supervisor of my PhD project and thereafter he has been my very valued leader at the Psychiatric Research Unit in Region Zealand. I want to thank Professor Erik Simonsen for always supporting my ideas and ambitions. I am very grateful to him, as he has given me the opportunity to work within this topic for ten years. Professor Erik Simonsen has taught me to see the value of true evidence-based psychiatry combining the external evidence with patient preference and clinical experience.

In 2009, Professor Erik Simonsen introduced me to another important mentor: Christian Gluud who is the leader of Copenhagen Trial Unit. Christian has been an excellent skilled teacher, who has always been available to answer my questions, always been very curious and willing to discuss any research topic at any time. My cooperation with Christian Gluud has been very encouraging and inspiring to me. Thank you for being a true mentor. I owe you everything.

I would also like to thank all my co-workers for our collaboration on the project investigating the benefits and harms of methylphenidate for children and adolescents with ADHD. I would especially like to thank all the young pregraduate students who have been working on this project. Thank you all for your contribution to this work.

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Finally, I would like to thank my friends and family for their support and my wife Bente for her patience and trust in me.

This doctoral dissertation is dedicated to my wife Bente and my two children Hannah and Tobias.

1. List of publications included in the thesis

1. **Storebø OJ**, Rosendal S, Skoog M, Groth C, Bille T, Buch Rasmussen K, Simonsen E, Gluud C. Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents. Cochrane Database of Systematic Reviews 2012;5:CD009885. DOI: 10.1002/14651858.CD009885(1)
2. **Storebø OJ**, Ramstad E, Krogh H, Nilausen TD, Skoog M, Holmskov M, Rosendal S, Groth C, Magnusson FL, Moreira-Maia CR, Gillies D, Buch Rasmussen K, Gauci D, Zwi M, Kirubakaran R, Forsbøl B, Simonsen E, Gluud C. Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents. Cochrane Database of Systematic Reviews 2015;11. Art. No.: CD009885. DOI: 10.1002/14651858.CD009885.pub2.(2)
3. Holmskov M, **Storebø OJ**, Moreira-Maia CR, Ramstad E, Magnusson FL, Krogh HB, Groth C, Gillies D, Zwi M, Skoog M, Gluud C, Simonsen E. Gastrointestinal adverse events according to type, dose, and duration of methylphenidate administration in children and adolescents with attention deficit/hyperactivity disorder – a meta-analysis with Trial Sequential Analysis. PloSOne 2017;12(6):e0178187 doi.org/10.1371/journal.pone.0178187(3)
4. Ramstad E, **Storebø OJ**, Gerner T, Krogh HB, Holmskov M, Magnusson FL, Moreira-Maia CR, Skoog M, Groth C, Gillies D, Zwi M, Kirubakaran R, Gluud G, Simonsen E. Hallucinations and other psychotic symptoms in response to methylphenidate in children and adolescents with attention deficit hyperactivity disorder: a Cochrane systematic review with meta-analysis and trial sequential analysis. Scandinavian Journal of Child and Adolescent Psychiatry and Psychology 2018;6(1):52-71. DOI: https://doi.org/10.21307/sjcapp-2018-003(4)
5. Krogh HB, **Storebø OJ**, Faltinsen E, Todorovac A, Ydedahl-Jensen E, Magnusson FL, Holmskov M, Gerner T, Gluud C, Simonsen E. Methodological advantages and disadvantages of parallel and crossover randomised clinical trials on methylphenidate for attention deficit hyperactivity disorder: a systematic review and meta-analyses. BMJ Open 2019;9(3):e026478.(5)
6. **Storebø OJ**, Pedersen N, Ramstad E, Krogh HB, Moreira-Maia CR, Magnusson FL, Holmskov M, Danvad Nilausen T, 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 hyper activity 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(6)
7. **Storebø OJ**, Pedersen N, Ramstad E, Kielsholm M, Nielsen S, Krogh HB, Moreira-Maia CR, Magnusson FL, Holmskov M, Gerner T, Skoog M, Rosendal S, Groth C, Gillies D, Buch Rasmussen K, Gauci D, Zwi M, Kirubakaran R, 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 2018, 5, CD012069. Published online 2018 May 9. doi: 10.1002/14651858.CD012069.pub2(7)

8. **Storebø OJ**, Zwi M, Krogh HB, Moreira-Maia CR, Holmskov M, Gillies D, Groth C, Simonsen E, Gluud C. Evidence on methylphenidate in children and adolescents with ADHD is in fact of 'very low quality'. Perspectives article, Evidence- Based Mental Health 2016;19:100-102, DOI:10.1136/eb-2016-102499(8)
9. **Storebø OJ**, Faltinsen E, Zwi M, Simonsen E, Gluud C. The jury is still out on the benefits and harms of methylphenidate for children and adolescents with attention-deficit/hyperactivity disorder. Clinical Pharmacology & Therapeutics 2018;104:606-9. doi:10.1002/cpt.1149(9)
10. Faltinsen E, Zwi M, Castells X, Gluud C, Simonsen E, **Storebø OJ**. Updated 2018 NICE guideline on pharmacological treatments for people with ADHD: a critical look BMJ Evidence-Based Medicine 2019;24:99-102. DOI: 10.1136/bmjebm-2018-111110(10)

The above papers number 1, 2, and 6 to 10 and results herein have not previously been submitted with the intention of acquiring an academic degree. Papers number 3 to 5 have previously been used by their first authors, who were all affiliated with the Psychiatric Research Unit, to fulfill their master's degree in medicine.

2. General introduction

2.1 About attention deficit hyperactivity disorder in children and adolescents

Attention deficit hyperactivity disorder (ADHD) is a commonly diagnosed and treated childhood neurodevelopmental disorder (11). The prevalence is about 3% to 8% of children and adolescents (12-14). The prevalence is depending on the classification system used, boys are more likely to be diagnosed than girls (two to four times) (15). The core symptoms of ADHD are difficulties with paying attention, impulsivity, and hyperactivity. Children and adolescents with ADHD often also have problems with cognitive functions such as problem-solving, flexibility, and working memory (16, 17). Children and adolescents with ADHD also often display difficulties with handling motivational delay and mood regulation (15, 18, 19).

The diagnosis of ADHD consists of inattention, and/or hyperactivity alongside impulsivity. These problems often reduces social, academic, or occupational functioning (20, 21). There are 18 core symptoms of ADHD according to the principal diagnostic classification systems: International Classification of Diseases - 10th Revision (ICD-10; (20) and the Diagnostic and Statistical Manual of Mental Disorders (DSM) - 4th Edition (22), - 4th Edition - Text Revision (23), and- 5th Edition (21).

Both the DSM-5 and ICD-10 criteria require that symptoms are pervasive and inconsistent with the developmental stage. The symptoms must be present in two or more settings, appear before the age of six years according to the ICD-10 (20), or before 12 years according to the DSM-5 (21), and also persist for at least six months. The DSM-5 has subsequently modified the criteria for adolescents and adults older than 17 years of age, with the need of fewer perceived symptoms and with the inclusion of further descriptions to more easily recognize typical ADHD symptoms in adolescents.

Earlier versions of the DSM-5 and the ICD-10 required clear evidence of clinically significant impairment in social, academic, and occupational functioning(20-22), but the DSM-5 only requires that symptoms decrease the quality of these domains (21). Also, the ICD-10 and the DSM-IV deviate from the newer DSM-5 by excluding people with autism spectrum disorder. DSM-5 states

that ADHD symptoms must not occur during the course of schizophrenia or another psychotic disorder and must not be better explained by another mental disorder (21).

There are different sub-diagnoses in both systems, in which specific symptoms are identified. In the DSM-IV-TR, these subtypes were named according to the predominant symptoms: 'predominantly inattentive type', 'predominantly hyperactive-impulsive type', and 'combined type' – a combination of both hyperactive-impulsive and inattentive symptoms (14, 21).

The etiology of ADHD is not yet fully understood, yet it is considered to involve genetic, environmental and social risk factors. There is a high heritability ranging from 70% to 80%, which has been shown in family and twin studies (24). There are no sex differences in regard to heritability. ADHD can persist into adulthood due to genetic factors (24, 25). One study found that in as many as 40% of children with the disorder, ADHD persisted into adulthood (26).

Risk markers that can predict the persistence of ADHD into adulthood are severity of the disease, treatment, comorbid conduct disorder, and major depressive disorder (27).

A number of studies have investigated environmental risk factors for ADHD. Families living below the poverty level are more likely to have children and adolescents diagnosed with ADHD (28). In a Swedish study of 811,803 individuals, low family income in early childhood was highly related to ADHD (29). Other possible risk factors are low birthweight (30, 31), prematurity (32-34), maternal exposure to tobacco (35-37), and exposure to chemical elements like manganese and lead (38).

Children and adolescents with ADHD have an increased risk for a broad spectrum of comorbid conditions (39). A large register study found that 66% of the children and adolescents with ADHD had also a comorbid disorder. Fifty-six percent had also learning disorders, 23% sleep disorders, 20% had also oppositional defiant disorder and 12% anxiety disorder (39).

ADHD may co-occur with bipolar disorder (40). Children with ADHD may also have comorbid problems with increased weight and obesity (41, 42).

ADHD comorbidity that involves a conduct disorder might lead to worse outcomes in academic achievement, criminality, and substance use (43-45). A prospective follow-up study found that children with ADHD had a higher risk compared with the normal population for developing schizophrenia in adulthood (46).

In addition, ADHD is associated with several serious prognostic consequences. A cohort of participants with ADHD followed for a long period demonstrated that these individuals have an elevated risk of death before 40 years of age (47, 48). ADHD can also increase the risk of accidents, social disability and addictions (45). In a Danish cohort study, patients with ADHD displayed during follow up (24.9 million person-years) an increase above 50% in premature mortality, compared to non-ADHD patients (49). ADHD is associated with considerable costs (50).

2. 2 Methylphenidate

Stimulant medication such as methylphenidate and dexamphetamine (or dextroamphetamine), together with the selective noradrenaline reuptake inhibitor atomoxetine (non-stimulant) and guanfacine (an alpha 2 agonist), are the recommended treatments of choice alongside psychosocial interventions for children and adolescents with ADHD (51-53).

Methylphenidate is one of the most commonly prescribed drugs for ADHD and it has been used for more than 60 years (52, 54). Methylphenidate appears to have a positive effect in reducing the core symptoms in children and adolescents with ADHD (45). It is licensed for children aged six years and older. A large study including more than 154 million people from 14 countries showed that the prevalence of ADHD medication use among children showed an absolute increase per year ranging from 0.02% to 0.26% in the period from 2001 to 2015 (55).

The use of ADHD medications is discontinued in 13% to 64% of patients of all ages (56). There is currently no information as to whether this discontinuation of treatment is mainly seen when patients transit from childhood to adolescence or from adolescence into adulthood.

Dexamphetamine is licensed for use in children from the age of three years old. It is also available as a pro-drug of dexamphetamine, named lisdexamphetamine. The latter has a longer duration of action than dextroamphetamine. Clinicians and families choose the most relevant medication based

on the presence of comorbid conditions, possible adverse events, and also issues on compliance, and what the child and family prefer.

The dosage of methylphenidate for ADHD varies from patient to patient. Individualized titration needs to take benefits and adverse events into consideration (57). The methylphenidate dosage per day varies from 5 mg to 60 mg, given one to three times per day, depending on the release system (immediate, sustained, or extended release) and also mode of administration (oral or transdermal) (53, 58). The British National Formulary suggests an initial dose of 2.5 mg twice daily for children aged four to six years old. It may be increased when necessary at weekly intervals by 2.5 mg daily, to a maximum of 1.4 mg/kg daily (spitted into several doses per day) (59). In children aged six to 18 years, the initial dose may be 5 mg once or twice daily. If necessary, this may be increased at weekly intervals by 5 mg to 10 mg daily, divided into two or three dosages. Methylphenidate is licensed to a maximum dose of 60 mg daily. However, under specialist supervision the dosage may be increased daily by 2.1 mg/kg, divided into two or three dosages, leading to a maximum daily dosage of 90 mg. The bioavailability of oral methylphenidate is 11% to 52%. The approximate duration of action is 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 (60).

The primary pharmacologic effect of methylphenidate is to increase central dopamine and norepinephrine activity. This is believed to increase the firing rate in synapses through increased neurotransmission of dopamine and noradrenaline, and this has an effect on the prefrontal cortex, which impacts executive and attentional function (61). The primary pharmacological effects of methylphenidate are related to increased norepinephrine and dopamine activity in cortex and striatum. These areas of the brain are related to regulation of attention and executive function (61). Due to this, patients might improve their overall function (through symptom control) and experience improved attention and reduced hyperactivity-impulsivity (62-67) which also may improve academic learning (68, 69). The European Network for Hyperkinetic Disorders (EUNETHYDIS) has reviewed the literature on adverse events of medications for ADHD. They conclude that there are adverse events due to stimulant medications, but that the balance of risk against possible benefits are mostly favorable. They also underline that there are several areas that require more research to more precisely understand the risk (70).

3. Aims and hypotheses

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

4. Summary of evidence of benefits and harms of methylphenidate up to 2014 from reviews

We performed a search in PubMed for reviews that assessed the effect of methylphenidate on ADHD symptoms in children and adolescents. We found fifteen reviews on the topic (71-85). All these reviews showed that methylphenidate improved ADHD symptoms and therefore the use of methylphenidate was recommended. However, there were several problems with these reviews which affected the validity of their conclusions. None of the reviews were conducted using Cochrane methodology and none of the reviews had a peer-reviewed protocol that had been pre-published. Accordingly, they were not systematic reviews. Many of them did not undertake analyses regarding comorbidity influencing treatment or considered the impact of dosage. Ten of them did not assess spontaneous adverse events and 11 did not report adverse events measured by rating scales. Nine reviews did not follow 'gold standard' guidelines, i.e., The Cochrane Handbook or the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA guidelines) (86-88). Trial quality were not systematically assessed in 11 of the reviews. Thirteen reviews excluded all non-English publications. Collectively, these limitations may have spoiled data collection and thereby the results and recommendations obtained (2).

5. Systematic Cochrane reviews on the benefits and harms of methylphenidate for children and adolescents with ADHD based on randomized clinical trials

Review 1: Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents (Papers 1-5)

5.1 Methods (Papers 1 and 2)

We included both parallel and crossover randomised clinical trials comparing all types of methylphenidate versus placebo or no intervention for children and adolescents with ADHD. Trials were included irrespective of language, publication year, publication type, or publication status. After the exclusion of duplicates and studies that clearly did not meet the inclusion criteria, full-text articles were obtained as per protocol (Figure 1).

The ADHD diagnosis in relevant trials had to be in accordance with the Diagnostic and Statistical Manual of Mental Disorders version III, version III revised or version IV (DSM-III, DSM-III-R and DSM-IV, DSM-IV-TR, DSM-5), or according to the International Classification of Diseases version 9 or version 10 (ICD-9, ICD-10). At least 75% of the participants had to be < 19 years and the mean age of the study population had to be < 19 years. We included trials where participants had comorbidities. At least 75% of the participants needed to have an intellectual quotient in the normal range (IQ > 70) (2).

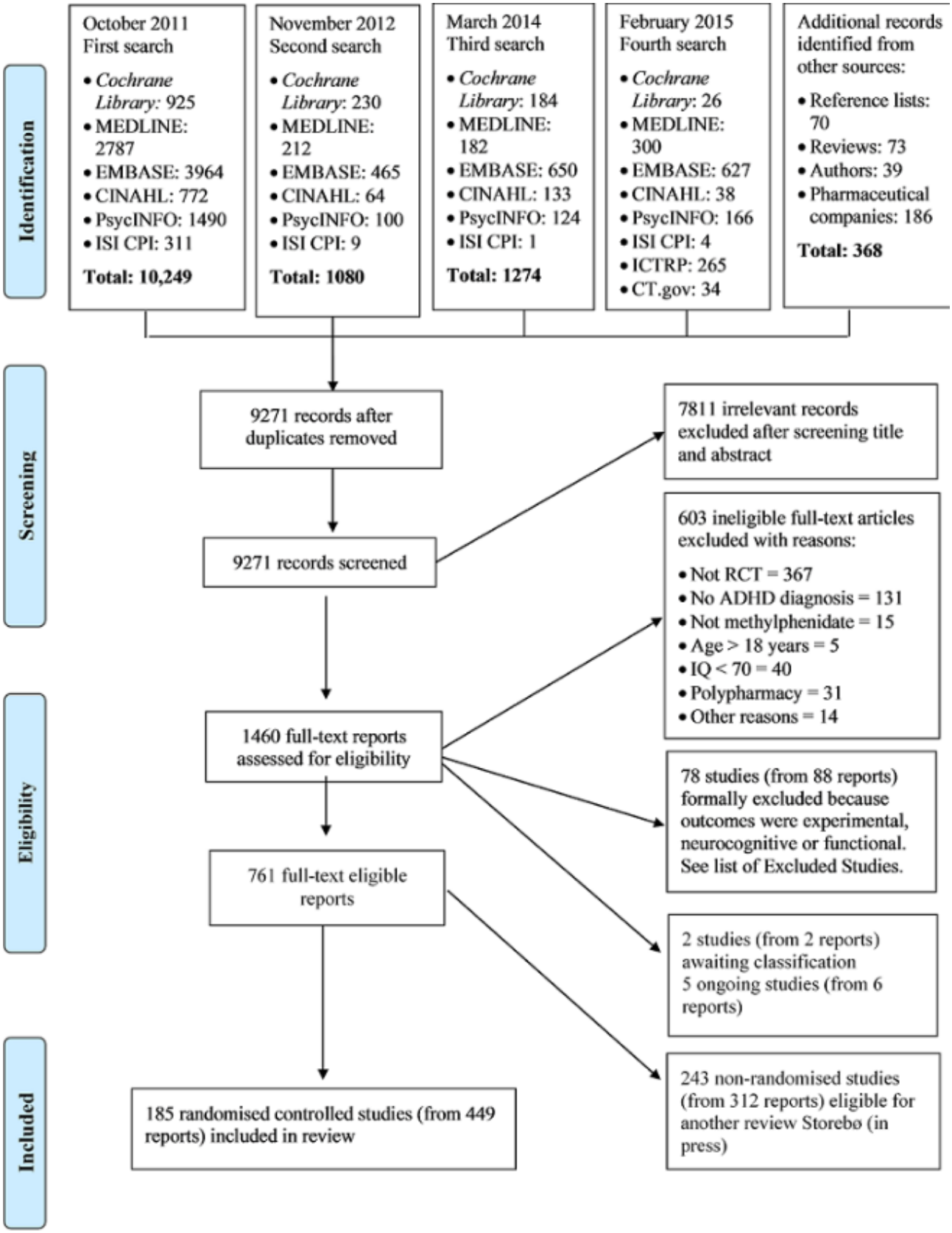
Identification
Screening
Eligibility
Included
October 2011
First search
• Cochrane Library: 925
• MEDLINE: 2787
• EMBASE: 3964
• CINAHL: 772
• PsycINFO: 1490
• ISI CPI: 311
Total: 10,249
November 2012
Second search
• Cochrane Library: 230
• MEDLINE: 212
• EMBASE: 465
• CINAHL: 64
• PsycINFO: 100
• ISI CPI: 9
Total: 1080
March 2014
Third search
• Cochrane Library: 184
• MEDLINE: 182
• EMBASE: 650
• CINAHL: 133
• PsycINFO: 124
• ISI CPI: 1
Total: 1274
February 2015
Fourth search
• Cochrane Library: 26
• MEDLINE: 300
• EMBASE: 627
• CINAHL: 38
• PsycINFO: 166
• ISI CPI: 4
• ICTRP: 265
• CT.gov: 34
Additional records identified from other sources:
• Reference lists: 70
• Reviews: 73
• Authors: 39
• Pharmaceutical companies: 186
Total: 368
9271 records after duplicates removed
9271 records screened
7811 irrelevant records excluded after screening title and abstract
603 ineligible full-text articles excluded with reasons:
• Not RCT = 367
• No ADHD diagnosis = 131
• Not methylphenidate = 15
• Age > 18 years = 5
• IQ < 70 = 40
• Polypharmacy = 31
• Other reasons = 14
1460 full-text reports assessed for eligibility
78 studies (from 88 reports) formally excluded because outcomes were experimental, neurocognitive or functional. See list of Excluded Studies.
761 full-text eligible reports
2 studies (from 2 reports) awaiting classification
5 ongoing studies (from 6 reports)
243 non-randomised studies (from 312 reports) eligible for another review Storebø (in press)
185 randomised controlled studies (from 449 reports) included in review

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart (The figure is reprinted from Storebø 2015 with the permission from publisher Wiley).

We searched many databases; MEDLINE, EMBASE, CINAHL, PsycINFO, ISI Conference Proceedings Citation Index- Science and Conference Proceedings Citation Index-Social Science & Humanities (Web of Science), ClincalTrials.gov and WHO's International Clinical Trials Registry Platform (ICTRP). The search was performed up to February 2015 using two different search strategies, one for efficacy and one for adverse events. The complete search strategy is available in the Cochrane review (2). We screened reference lists of identified reviews, meta-analyses as well as a selection of included trials which was identified in other relevant articles. Furthermore, we contacted Shire, Medice (represented in Denmark by HB Pharma), Janssen-Cilag, and Novartis, which all are producing methylphenidate for published and unpublished data. We were requesting data on unpublished or ongoing studies by emailing experts in the field (2).

The primary outcomes were ADHD core symptoms and serious adverse events.

5.1.1 Analyses

Data were summarized and dichotomous data was presented as risk ratios (RR) with 95% confidence intervals (CI). Continuous data were presented as mean difference (MD) between groups, also including a 95% CI. We calculated the standardized mean difference (SMD), if different scales were used to assess the same outcome in the included trials. To assess the minimal clinically relevant difference (MIREDIF), we transformed the SMD on selected outcomes into a corresponding MD of a relevant scale with a known published MIREDIF. As far as we know, the only published MIREDIF relevant to our selected outcomes includes 6.6 points for the ADHD-RS (ADHD symptoms, the scale ranging from 0 to 72 points) (89) and 7.0 points for the Child Health Questionnaire (quality of life, the scale ranging from 0 to 100) (90). We included several trials with a crossover design. We contacted the authors of these trials in the attempt to acquire sufficient data from the first trial period, as we wanted to meta-analyze these particular data with the data from the parallel group trials. Nevertheless, we only managed to receive first period data from a few crossover trials and therefore eventually the analyses were conducted with end of period data from the crossover trials. We had planned to adjust for unit of analysis error by conducting a covariate analysis; however, we did not have the necessary data for this. Difference in treatment effects between data from parallel group trials and crossover trials was tested through further subgroup

analyses, as we expected to find a variation between these two study designs, due to both carry over effects and unit of analysis errors (91). We did not find any notable difference between the two study designs; however, we still did not pool this data due to high heterogeneity between subgroups. Results were therefore presented in separate analyses. We dealt with missing data by contacting the authors of the trials and asking for further information. If we were not able to obtain any additional data from the authors, the analyses were conducted by using the available data in the respective publications (58). The random-effects model was used in all meta-analyses, and the fixed-effect model in the sensitivity analysis (2).

5.1.2 Subgroup analyses

We conducted the following subgroup analyses:

1. Type of scales used to assess a given outcome.
2. Age of the participants (trials with participants aged two to six years compared to those with participants aged seven to 11 years compared to those with participants aged 12 to 18 years).
3. Sex (boys compared to girls).
4. Comorbidity (children with comorbid disorders compared with children without comorbid disorders).
5. Type of ADHD (participants with predominantly inattentive subtype compared with participants with combined subtype).
6. Duration of treatment (short-term trials (≤ six months) compared to long-term trials (> six months).
7. Risk of bias (trials with low risk of bias versus trials with high risk of bias).
8. Dose of methylphenidate (low dose ≤ 20 mg/day or ≤ 0.6 mg/kg/day compared to moderate/high dose > 20 mg/day or > 0.6 mg/kg/day).
9. Design (parallel trial compared to first phase and end-of-trial crossover trials).
10. Medication status before randomization, i.e. ‘medication naïve’ (if more than 80% of participants were naïve) compared to ‘previously exposed’ to medication (more than 80% of participants previously exposed).
11. Types of raters − parent raters compared to observer raters compared to teacher raters.
12. Trials with cohort selection bias of all participants compared to trials without cohort selection bias of all participants.
13. Trials with fixed doses compared to trials with initial titration.

5.1.3 Sensitivity analyses

We conducted sensitivity analyses to ascertain whether our findings were sensitive to:

1. Decisions made during the review process, e.g. our assessment of clinical heterogeneity.
2. 'Change scores' and 'end of trial' scores combined in one meta-analysis.
3. Inclusion of studies whose participants had IQ < 70 or age > 18 years.
4. Difference when applying fixed-effect models compared to the random-effects models.

5.1.4 Trial Sequential Analysis

Equivalent to performing a sample size calculation when conducting a randomised clinical trial, a frequentist meta-analysis should also include a calculation of the required information size (RIS) that is needed to reduce the risk of type two and type one error. Trial Sequential Analysis (TSA) is a software program used to calculate the required information size for a meta-analysis, which also includes adjusted statistical thresholds for benefits, harms, or futility before the required information size is reached. Meta-analyses are analyzed with trial sequential monitoring boundaries similar to interim monitoring boundaries in a single trial. If a TSA result is found to be insignificant before RIS has been reached the conclusion should be that more trials are needed in order to accept or reject the intervention effect. The anticipated intervention effect can be rejected if the cumulated Z-curve enters the futility area (92-98).

For TSA calculations concerning binary outcomes, we included zero event trials by substituting zero with 0.5.

For the outcomes, 'total serious adverse events' and 'total non-serious adverse events', we calculated the number of patients required to detect or reject a specific intervention effect in the meta-analysis. The a priori diversity-adjusted required information size (DARIS) on the following assumptions: the proportion of patients in the control group with adverse events; a relative risk reduction or increase of 20%; a type I error of 5%; a type II error of 20%; and the observed diversity of the meta-analysis (92-98). *"We defined serious adverse events, as any event that led to death, were life-threatening, required in-patient hospitalization or resulted in persistent or significant disability, or as any important medical event that may have jeopardized the patient's life*

or that required intervention for prevention (99). *We considered all other adverse events as non-serious"* (99).

5.1.5 Quality of evidence

Authors evaluated all risk of bias domains independently, after which any potential disagreements were resolved by discussion. Each bias domain were assigned each to one of three categories: low risk of bias, uncertain risk of bias or high risk of bias, in accordance with Cochrane methodology guidelines (86).

The following risk of bias domains were assessed for each of the included trials: generation of allocation sequence, concealment of allocation, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and vested interest. The latter domain concerns trials that were funded by parties with a potential conflict of interest (e.g. a producer of methylphenidate) and/or trials including authors with potential conflicts of interests due to affiliation with companies producing methylphenidate.

We defined trials at low risk of bias as trials having low risk of bias in all domains. Trials with one or more unclear or inadequate component were considered as trials at high risk of bias (94). For 32% (59/185) of the included trials, we noted a specific type of bias which occurred prior to randomisation. In certain trials, there was an exclusion of non-responders towards methylphenidate, placebo responders, and/or patients that had adverse events due to the medication. Subgroup analyses were conducted, to identify whether this 'cohort selection bias of all participants' had an impact on effect estimates.

We graded the evidence in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which includes a collective assessment of high risk of bias, imprecision, indirectness, heterogeneity and publication bias (100-103).
The analyses were conducted using the Review Manager 5.3 (Review Manager 2014) and TSA program (104).

5.2 Main results (Paper 2)

We included 185 randomised clinical trials, 38 were parallel-group (n = 5111 participants) and 147 were cross-over (n = 7134 participants) trials. The total number of participants was 12,245. Participants of both sexes were included. All participants were between three and 21 years of age, with an average 9.7 years of age. Most of the trials were conducted in high-income countries. The median duration of treatment in parallel group trials was 49 days and 14 days in the crossover trial. All trials except six crossover trials were assessed at high risk of bias. Based on the GRADE approach, we rated the quality of evidence as being very low for the efficacy outcomes and low for the safety outcomes (2).

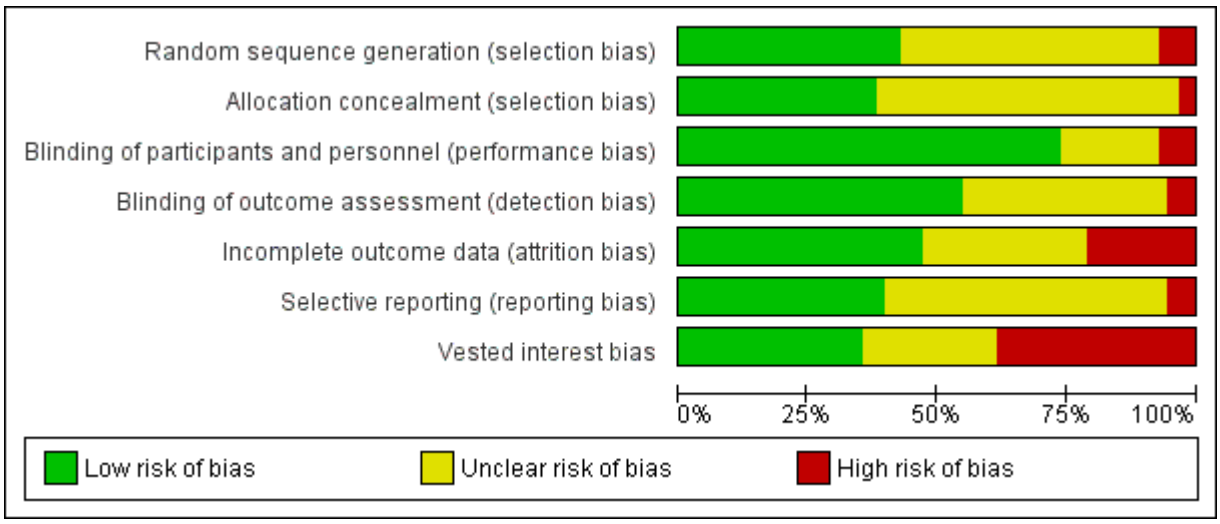

Figure 2. Risk of bias of all trials (The figure is reprinted from Storebø 2015 with the permission from publisher Wiley).
(Green: low risk of bias, Yellow: uncertain risk of bias, Red: high risk of bias)

5.2.1 ADHD core symptoms

In the parallel trials, we found a small effect of methylphenidate on teacher-rated ADHD symptoms (SMD -0.77, 95 % CI -0.90 to -0.64, 19 trials, 1698 participants, P < 0.00001, I^2 37%). This effect corresponds to a mean difference of -9.6 points (95% CI -11.25 to -8.00) on the Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS), which thus exceeds the minimal important clinical relevant difference (MIREDIF) of -6.6 points for this particular scale. There were no indications of publication bias (Egger's test P = 0.81). All the trials were assessed at high risk of bias. The GRADE assessment was rated as being 'very low certainty' due to high risk of bias,

heterogeneity, and selective outcome reporting. There was a significant difference between the types of scales being used (test for subgroup differences, P = 0.006) and we found that long-term trials had a smaller effect (SMD -0.47, 95% CI -0.72 to -0.22, 1 trial, 253 participants) compared to short-term trials (SMD -0.81, 95%, CI -0.94 to -0.68, 18 trials, 1445 participants; test of subgroup difference, P = 0.02). Trials which included patients with a prior treatment experience displayed a higher treatment effect (SMD -1.06, 95% CI -1.33 to -0.79, 2 trials, 286 participants) as compared to trials that included medication naïve patients (SMD -0.63, 95 % CI -0.94 to -0.31, 4 trials, 431 participants; test for subgroup difference, P = 0.04). The subgroup analyses showed no apparent influence on treatment effect, when investigating the influence of trial design, cohort selection bias, and trials with initial titration or fixed doses. The end of last period crossover trials showed a significant treatment effect with SMD of -0.93 (95% CI -1.06 to -0.80, 59 trials, 5145 participants, P < 0.00001, I^2 77 %) (2).

5.2.2 Additional subgroup analyses

When performing additional subgroup analyses investigating the impact on ADHD symptoms in both parallel group trials and during the first period of crossover trials, we found that neither age or comorbidity significantly influenced the intervention effect. We found no evidence of a 'carry-over effect' between the first and second period data reported in crossover trials (first period; SMD -0.64, 95% CI -0.85 to -0.44, and second period; SMD -0.91, 95% CI -1.18 to -0.65, 4 trials, 372 participants; test for subgroup difference P = 0.1) (2).

We furthermore did not identify any significant difference in treatment effects, when this was assessed by various raters, including teachers (SMD -0.78, 95 % CI-0.93 to-0.63, 19 trials, 1689 participants), observers (SMD -0.61, 95 % CI -0.87 to -0.35, 9 trials, 1826 participants) and parents (SMD -0.65, 95 % CI -0.81 to -0.50, 21 trials, 2179 participants) (test for subgroup difference P = 0.37).

5.2.3 Serious adverse events

Serious adverse events were reported in nine parallel group trials (4.9%). In these trials, methylphenidate was not associated with an increase in the total number of serious adverse events (RR 0.98, 95% CI 0.44 to 2.22, 9 trials, 1532 participants, P = 0.97, I^2 0%). All nine trials were at high risk of bias due to vested interests, incomplete and selective outcome reporting, as well as lack

of sufficient blinding. The overall certainty of the evidence, as assessed by GRADE, was low due to high risk of bias. Eight crossover trials reported on serious adverse events during the last period of the trial. Results showed that there was no difference in the occurrence of serious adverse events between groups (RR 1.62, 95% CI 0.34 to 7.71, 8 trials, 1648 participants, P = 0.65, $I^2$0 %).
We conducted a TSA on methylphenidate versus placebo on the proportion of participants with the 'total serious adverse events' outcome. This outcome included the nine parallel group trials (Figure 3). The DARIS was calculated based on the serious adverse events proportion in the control group of 2 %; the relative risk reduction or increase of 25% in the experimental group; type I error of 5%; type II error of 20% (80% power); and a diversity (D-square) of 0%. The DARIS was 21,593 participants. The cumulative Z-curve did not cross the conventional or trial sequential monitoring boundaries for benefit, harm, or futility. As the DARIS was not reached, the risks of random error cannot be excluded. Therefore, the total sample size in the meta-analysis relating to serious adverse events of 1532 participants was considerably underpowered (58).

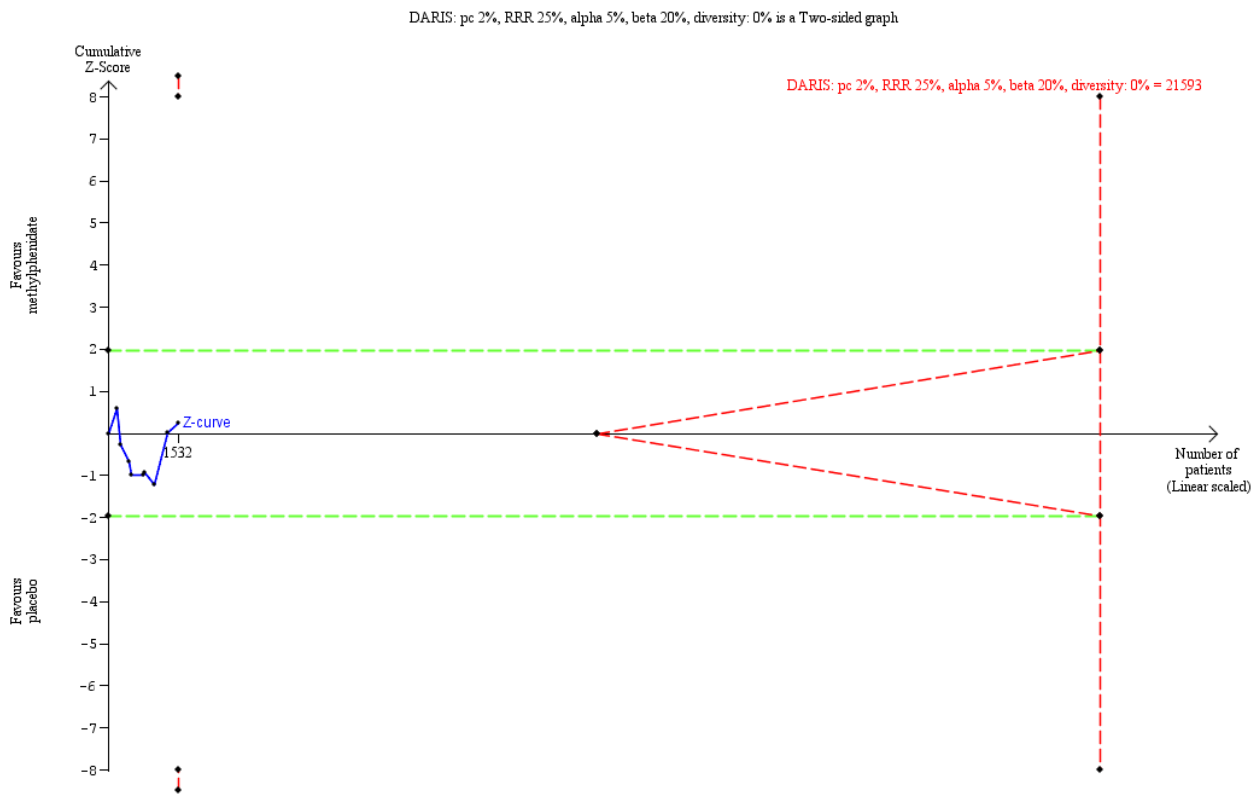

Figure 3.Trial Sequential Analysis (TSA) of methylphenidate versus placebo on proportion of ADHD participants with serious adverse events. DARIS is the diversity-adjusted required information size (The figure is reprinted from Storebø 2015 with the permission from publisher Wiley).

5.2.4 Non-serious adverse events

The various adverse events reported in the individual trials included urinary, neurological, respiratory, digestive, circulatory, reproductive, skeletal, muscular and immunological adverse events. Results showed, that methylphenidate led to an increase in the total non-serious adverse events by 29% (RR 1.29, 95% CI 1.10 to 1.51, 21 trials, 3132 participants). As assessed by the GRADE approach, the certainty of this estimate was low, due to high risk of bias, heterogeneity, and selective outcome reporting. We further assessed the impact of methylphenidate on physical measures such as difference in height, weight, body mass index and vital signs. The most common non-serious adverse event was a decrease in appetite (RR 3.66, 95% CI 2.56 to 5.23, 16 trials, 2962 participants; I^2 28%) and sleep problems (RR 1.60, 95% CI 1.15 to 2.23, 13 trials, 2416 participants; I^2 0%).

The occurrence of non-serious adverse events was also reported in sixty-five crossover trials during the end of the second period. Here, methylphenidate was associated with an increase in total number of non-serious adverse events (RR 1.33, 95% CI 1.11 to 1.58; 21 trials, 2072 participants; I^2 18 %), with the most common adverse events being a decrease in appetite (RR 3.04, 95% CI 2.35 to 3.94, 35 trials, 3862 participants, I^2 40%) and sleep problems (RR 1.57, 95 % CI 1.20 to 2.06, 31 trials, 3270 participants, I^2 47%).

The total number of non-serious adverse events was reported as an outcome in 21 trials, which included both parallel group trials and cross-over trials at the end of first period (Figure 4). To investigate this further, we conducted a TSA on the proportion of participants presenting with the 'total non-serious adverse events' outcome (Figure 4). The DARIS included 4133 participants and was calculated based on a proportion of 47% adverse events in the control group, a 20% relative increase or reduction in the experimental group; 5% type I error; 20% type II error (80% power); and a 79% diversity (D-square).

Results showed that after the seventh trial, the cumulative Z-curve (blue line) crossed the trial sequential boundary for harm (red inward sloping line). It then regressed and at the 17th trial crossed the boundary again, after which it never regressed. The TSA-adjusted RR was 1.29 (95 %

CI 1.06 to 1.56). Based on these findings, we can exclude that the result concerning non-serious adverse events is a cause of random error (2).

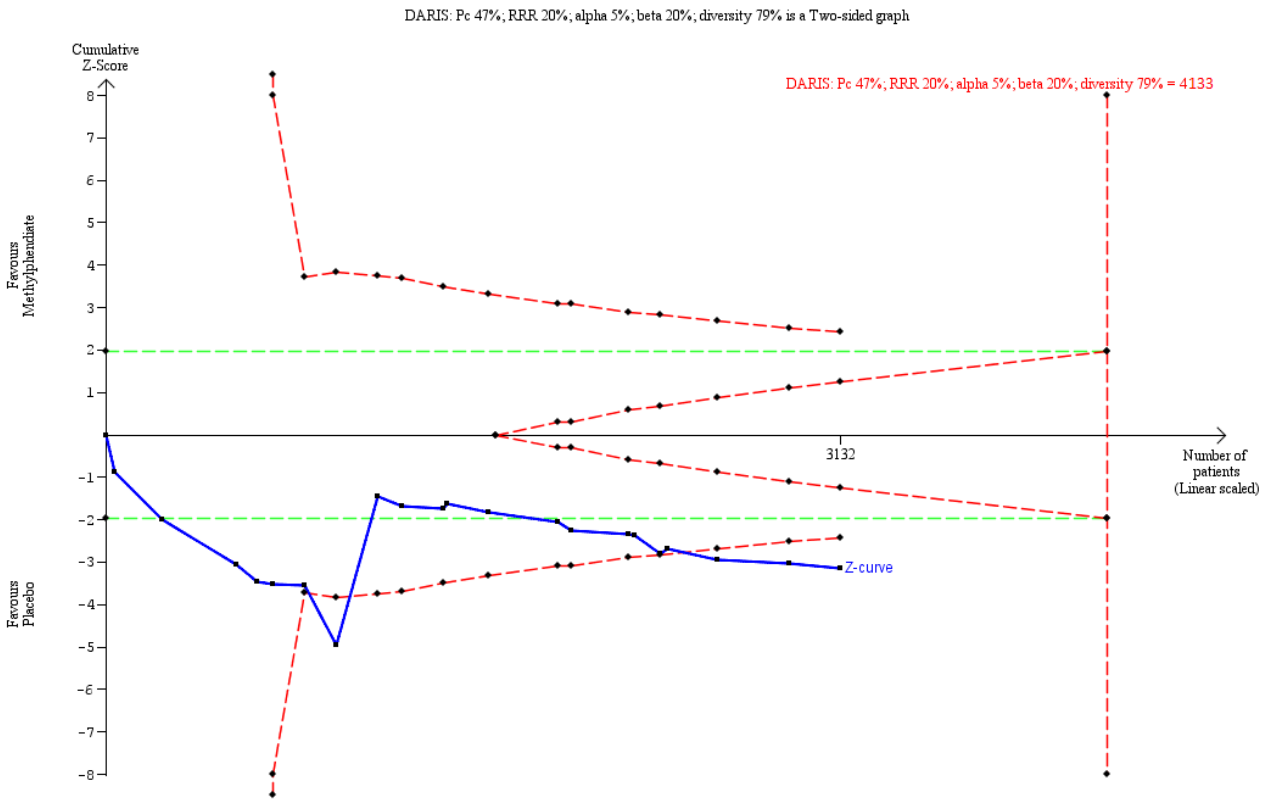

Figure 4. Trial Sequential Analysis (TSA) of methylphenidate versus placebo or no intervention on proportion of ADHD participants with non-serious adverse events. DARIS is the diversity-adjusted required information size. (The figure is reprinted from Storebø 2015 with the permission from publisher Wiley).

5.2.5 General behavior

Seven parallel group trials and 18 crossover trials reported on general behavior. The analysis of teacher-rated general behavior in parallel trials resulted in (SMD -0.87, 95 % CI -1.04 to -0.71, 5 trials, 668 participants), which represents improvement. It was not possible to transform this estimate into a widely used validated scale. The certainty of the identified estimate, as assessed by GRADE, was very low due to high risk of bias, indirectness, and selective outcome reporting. Further analysis showed that the intervention effect was not significantly influenced by the type of scale or dosage being used in the respective trials. The analysis of the crossover trials also showed a beneficial treatment effect, with (SMD -0.69, 95% CI -0.78 to -0.60, 16 trials, 2014 participants),

which was not influenced when different dosage of methylphenidate was applied. All the included crossover trials were considered to have high risk of bias (2).

5.2.6 Quality of life

Three parallel group trials (1.6%) reported on quality of life. There was a small beneficial effect on quality of life (SMD 0.61, 95% CI 0.42 to 0.80, 3 trials, 514 participants), which corresponds to a mean difference of 8.0 points (95% CI 5.49 to 10.46) on the Child Health Questionnaire scale (CHQ). This exceeds the MIREDIF of 7.0 for this particular scale. However, the estimate relies on only three trials, with all three trials displaying high risk of bias, primarily due to lack of blinding of participants and vested interest. The GRADE assessment was ’very low certainty’ due to high risk of bias, indirectness, and selective outcome reporting (2).

5.3 Results on gastrointestinal adverse events (Paper 3)

Based on the Cochrane review from 2015 (2), the purpose of this study was to thoroughly investigate the relationship between the use of methylphenidate and the risk of gastrointestinal adverse events in children and adolescents with ADHD (3). As such, post hoc analyses were conducted based on the data from the large review from 2015. A total of 18 parallel group trials and 43 crossover trials were included. All trials were considered at high risk of bias.

The analysis from the parallel group trials showed that methylphenidate was associated with the risk of a decrease in appetite (RR 3.66, 95% CI 2.56 to 5.23, 16 trials, 2962 participants). Further investigations showed that methylphenidate neither increased nor decreased the risk of the following adverse events: diarrhea, dyspepsia, increased appetite, nausea, abdominal pain, and vomiting. There were no differences in gastrointestinal adverse events, when investigating the effect of different types of methylphenidate. We found no differences in adverse events as a consequence of different dosages, except for a significant decrease in appetite when a moderate/high dose was applied. Furthermore, we found no differences in the risk of gastrointestinal adverse events due to the duration of the trials.

In the crossover trials, we found that methylphenidate compared to placebo decreased appetite (RR RR 3.04, 95% CI 2.35 to 3.94, 35 trials, 3862 participants; I2 = 40%); compared to placebo) and increased abdominal pain (RR 1.61, 95% CI 1.27 to 2.04, 33 trials, 1837 participants). There were

no significant differences when comparing the risk for various gastrointestinal adverse events when different types or dosage of methylphenidate were applied. For the crossover trials, it was not possible to investigate the impact of trial duration, due to lack of data.

We found no evidence of publication bias for the majority of the investigated outcomes, except for possible publication bias for the outcome on decreased appetite. The TSA software was used to further assess the following outcomes: decreased appetite, nausea, abdominal pain and vomiting. The TSA showed that the cumulative Z score crossed the trial sequential boundaries for harm and therefore the risk of random errors can be excluded for the outcome concerning decreased appetite. For the outcomes nausea and vomiting, the cumulative Z score crossed into the areas of futility and therefore showed no need for conducting further trials when the RRR of 10 %, an alpha of 5 % and a beta of 20 % were used. For the outcome abdominal pain, the required information size and the futility area were not reached and therefore the risk of type 1 or type 2 error cannot be excluded.

5.4 Results on the adverse event psychosis (Paper 4)

The purpose of this study was to investigate the occurrence of psychotic symptoms in children and adolescents with ADHD while being treated with methylphenidate (4). A post hoc analysis was conducted based on the data from the large review from 2015 (2). Here psychosis was reported in four of the parallel - and six of the crossover randomised trials. Seventeen non-randomised studies as well as 12 case studies were also identified. In all the randomised trials, there was no difference regarding the risk of developing psychosis during methylphenidate treatment (RR 2.07, 95% CI 0.58 to 7.35, 10 trials, 1049 participants, P = 0.26; I^2 0%). All the trials were considered at high risk of bias and the certainty of the evidence was rated as low, due to high risk of bias and imprecision. The TSA analysis showed that the required information size was not reached and therefore risk of random error cannot be excluded. In the non-randomised studies, there were 873 instances of psychotic symptoms among 55,603 participants, which gave a pooled prevalence of 1.2% (95% CI 0.7 to 2.4). Eighteen patients were included in the 12 case studies, of which 16 of the patients had developed a psychosis while being treated with methylphenidate.

5.5 Differences between crossover trials and parallel group trials (Paper 5)

The purpose of this study was to assess the methodological advantages and disadvantages of parallel and crossover design in randomised clinical trials on methylphenidate treatment in children

and adolescents with ADHD (5). Data from the large 2015 review was used and post hoc analyses were conducted (2). The primary outcomes in this study were teacher-rated ADHD core symptoms and serious adverse events. The secondary outcomes were non-serious adverse events. Thirty-eight parallel group trials and 147 crossover trials were included. For the primary outcome teacher-rated ADHD symptoms, we found no difference between the end of parallel trials and first period of the crossover trials (x^2 = 1.06, df = 1, P = 0.30, 19 trials, 1601 participants). The same results were found when this particular outcome was rated by parents (x^2 = 0.00, df = 1, P = 0.96, 21 trials, 2187 participants) and observers (x^2 = 0.30, df = 1, P = 0.58, 10 trials, 1907 participants). We found no difference when comparing parallel group trials plus first period crossover trials, with end of the second period in the crossover trials (x^2 = 3.25, df = 1, P = 0.07, 75 trials, 6247 participants). When investigating serious and non-serious adverse events, we found no difference between the end of parallel group trials and the end of the second period crossover trials (serious adverse events: x^2 = 0.31, df = 1, p= 0.58, 17 trials, 3253 participants; non-serious adverse events X^2 = 1.45, df = 1, P = 0.23, 20 trials, 3132 participants).

5.6 Discussion (Papers 1 to 5)

Methylphenidate seems to reduce ADHD core symptoms as well as improve quality of life and improve general behavior. The effects of methylphenidate on both the ADHD-RS and the CHQ scales seem to be clinically relevant based on our predefined minimal relevant differences. However, our results have 'very low certainty' when assessed by the GRADE instrument, and all results may have been caused by methodological bias.

We do not know whether the use of methylphenidate can cause an increased risk of serious adverse events in the short term due to low reporting on this outcome. The data on serious adverse events was underpowered as shown by the TSA analysis. There was also no data available from randomised trials on the long-term incidence of serious adverse events. We found a relatively high risk of non-serious adverse events. Over 25% of the children appear to experience non-serious adverse events during methylphenidate treatment. Adverse events are often underreported in randomised clinical trials, and they are often difficult to measure because of the short time span of most clinical trials (105). We found a high risk for decrease in appetite. We considered this a non-serious adverse event, but in fact, this adverse event can be serious for developing children. We found no increased risk of psychosis during methylphenidate treatment in parallel group trials, but

in the non-randomised studies we found a pooled prevalence of 1.2 % (95 % CI 0.7 to 2.4) (4). Eighteen patients were included in the 12 case studies, of which 16 of the patients had developed a psychosis while being treated with methylphenidate. Both parallel and crossover trials seems suitable to investigate the benefits and harms of methylphenidate in children and adolescents with ADHD as the effect sizes are comparable on both the benefit outcomes and the harms. We do, however, believe that parallel trials might offer ethical and statistical favors over crossover trials. Causality of harms and effects in crossover trials and may be difficult to determine, and there may be unknown adverse events associated with exposing participants to multiple interventions in a trial (5).

Our findings should be considered in light of the low certainty of the included trials due to avoidable methodological limitations such as inadequate sequence generation and allocation concealment, lack of blinding, performance bias, detection bias, selection bias, attrition bias, reporting bias, and possible bias caused by vested interest (106, 107).

Only six of 185 trials appeared at low risk of bias in all domains. We believe, however, that even these six trials at low risk of bias may in fact be trials at high risk of bias due to lack of blinding. We do so as the intervention effects in these trials mirrored those of the trials at high risk of bias. There is evidence showing that lack of blinding can give overestimated beneficial treatment effects (108). As methylphenidate gives rise to a number of easily recognizable adverse events (more than placebo does), it can lead to loss of blinding and influence the rating of symptoms and adverse events. At the same time, participants on placebo do not feel anything while consuming placebo, so blinding tend also to be lost in this group. Similar problems are seen with antidepressants in depressed patients (109, 110).

In 2015, this review was the most comprehensive systematic review and meta-analysis of ADHD treatment with methylphenidate for children and adolescents. We concluded that there might be a beneficial effect of methylphenidate treatment on ADHD core symptoms, general behavior, and quality of life. However, we were not certain about these effects. We also found there might be no risk of serious adverse events but that we could not assess this due to few trials and low power in the analysis. We also found that there was a considerable risk for non-serious adverse events. When comparing this review to other reviews published up to 2015, we found that almost all the

previously published reviews concluded that there was a large effect of treatment with methylphenidate. However, all these reviews had several shortcomings as described above. Most of them did not assess the risk of bias of the included studies or evaluated the effects of methylphenidate on adverse events. None of these reviews considered the risks of random errors. None of them had a pre-published protocol, so they did not qualify as 'systematic reviews'. Therefore, we believe that the true estimate of the treatment effects of methylphenidate is unknown, and information about adverse events from several randomised clinical trials is missing. The short duration of the included trials is also a problem. The median duration of treatment in parallel group trials was 49 days and 14 days in the crossover trials. This means that we know very little about the evidence for periods longer than a couple of months. This is a problem as most patients are treated for years.

5.7 Strength and limitations

For this review, we developed a protocol, which was peer reviewed and published before the work with the review itself was initiated. We conducted searches in relevant databases, as well as requested data from pharmaceutical companies. The selection of trials to be included and the following data extraction was performed independently by two review authors. Disagreements were resolved by discussion with additional team members. We assessed risk of bias in all included trials, by following the recommendations stated in the Cochrane Handbook for Systematic Reviews of Interventions.

It is a limitation that we did not search the databases of the US Food and Drug Administration and European Medicines Agency for unpublished trials (111). However, such unpublished clinical study reports usually contain more trials without treatment benefits and more adverse events. Moreover, vested interests should have been considered as a potential contributor to publication bias. The latter would only lead to further downgrading of the evidence.

5.8 Conclusions

Children and adolescents receiving methylphenidate may experience improvement of the symptoms of ADHD, general behavior, and quality of life. Methylphenidate might not cause an increased risk of serious adverse events in the short term, but we cannot state that for sure, as there was high

underreporting of data on this. We know nothing on the risks of serious adverse events in the long term. Methylphenidate was associated with relatively high risk for non-serious adverse events. These findings should be interpreted in the light of the various limitations described above. There is a need for more long-term randomised active placebo-controlled clinical trials without risks of bias to allow firm conclusions regarding methylphenidate treatment in children and adolescents with ADHD. We suggest that active placebo-controlled trials should be conducted first in adults with ADHD.

6.0 Review 2: Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents – assessment of harmful effects in non-randomized studies (Papers 6 and 7).

We conducted the present review on non-randomised studies (6, 7) following the first Cochrane systematic review from 2015 (2), which was based on randomised clinical trials, as we wanted to extend our investigations to also include an assessment of the evidence on harms from non-randomised studies. The inclusion of non-randomised evidence is often necessary when seeking to evaluate long-term effects on harms. In addition, adverse events are often better reported in non-randomised studies (94, 112)

6.1 Method

6.1.1 Participants

This review (6, 7) was conducted in accordance with the procedures and standards described in The Cochrane Collaboration and PRISMA guidelines (86, 88, 113).

We included non-randomised clinical trials, comparative cohort studies, cohort studies, patient-control studies (previously called ‘case-control studies’), cross sectional studies, and patient reports. The included participants were children and adolescents diagnosed with ADHD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-III, DSM-III-R, DSM-IV, and DSM-V) (APA 2013, APA 1980, APA 1987, APA 1994), or with hyperkinetic disorders according to the International Classification of Diseases (ICD-9, ICD-10) (WHO 1978). Participants with and without comorbid conditions were included, with comorbidity involving disorders such as conduct

or oppositional disorders, tics, depression, attachment disorders, autism, and anxiety disorders. For a given trial, at least 75% of the participants were required to have normal intellectual capacity (IQ > 70), and at least 75% of the participants had to be under 19 years of age. The mean age of the overall study population had to be 18 years or younger (7).

We searched the Cochrane Central Register of Controlled Trials (The Cochrane Library 2016, Issue 1), Medline, Embase, CINAHL, PsycINFO, ISI Conference Proceedings Citation Index, Science and Conference Proceedings Citation Index-Social Science & Humanities (Web of Science), ClincalTrials.gov, NDLTD, and the WHO's International Clinical Trials Registry Platform up until January 2016. We contacted experts in the field and pharmaceutical companies for published and unpublished data and checked reference lists from relevant reviews, meta-analyses, and additional studies. Finally, we searched for unpublished data on the websites of the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (7).

6.1.2 Outcomes

The primary outcome was 'serious adverse events' (6, 7). Serious adverse events were defined as any life-threatening event or event leading to death, inpatient hospitalization, persistent/significant disability, or prolongation of an existing or persistent/significant disability. Any other important medical event that may have jeopardized a patient's life or required an intervention to prevent any of these outcomes, was also considered to be a serious adverse event (99).

Our secondary outcome was 'non-serious adverse events' (6, 7). This outcome involved all other adverse events, including, but not confined to, the following types: cardiac events, neurological events, appetite suppression, gastrointestinal events, sleep problems, and growth retardation (99).

Adverse events were measured during treatment, at the end of treatment, and at the longest recorded follow-up. The identification of adverse events was based on either physical or para-clinical examinations, by the use of rating scales or by spontaneous reporting by the investigators during regular interviews or visits.

6.1.3 Data collection and analysis

The inclusion and exclusion of studies, as well as data extraction was performed following a two-step process. Review authors worked together in groups of two, and independently screened titles, abstracts and full texts. Six authors subsequently entered the data into Review Manager.

Certainty assessment and risk of bias assessment of the included studies followed the Cochrane Collaboration's guidelines. We used Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) (114) to assess the potential for risks of bias, in comparative cohort studies and patient-control studies. Each study was assigned one of the following categories: 'low' 'moderate', 'serious', 'critical risk of bias', or 'no information'. We decided not to rate risk of bias in studies lacking a comparator group, since ROBINS-I is not designed for such study designs. All studies without a valid or eligible comparator group were considered to encompass critical risk of bias.

The dichotomous data from the trials were summarized as risk ratios with 95 % confidence intervals (CI). Risk ratio (RR) was also used to evaluate harms. For continuous data, we calculated the mean difference (MD) between the two groups and presented it with 95 % CIs. If different continuous measures were used to assess the same outcome between trials, standard mean differences (SMDs) with 95% CI were used. We followed the Cochrane guidelines to calculate SDs if trials did not report means and standard deviations (SDs) but instead reported values as t-tests and P-values (94).

We used the inverse variance method when performing meta-analyses. This method gives more weight to larger studies, which reduces the imprecision in the pooled estimate of effect (94). The random-effects model was used in all meta-analyses, and the fixed effect model in the sensitivity analysis. We calculated pooled proportions from non-comparative studies.

We divided our analyses into two sections: one for comparative studies (patient-control studies and comparative cohort studies) and one for non-comparative studies. For the non-comparative studies, we further divided the adverse events into subgroups in accordance with the affected physiological system and analyzed the proportion of individuals with different adverse events under each system.

A few studies only reported data narratively. Due to high heterogeneity of the data, it was not possible to combine these in a meta-analysis. Patient reports were used to identify rare adverse

events according to the brand's Summary of medical Product Characteristics (SmPC) (115). When studies had combined designs, we assessed these separately. For comparative studies, meta-analyses were performed in accordance with the latest version of the Cochrane Handbook (94), and RRs were used to evaluate adverse events.

When reporting adverse events, we separated these into the categories 'serious', 'non-serious', and 'unknown', the latter being used whenever a study did not report the nature of the adverse event. We also reported the proportion of withdrawals due to adverse events.

6.1.4 Results

Four hundred thirty-one articles were included, covering 260 empirical studies with 2,283,509 patients. Four of these were patient-control studies (n = 74,183), six were comparative cohort studies (n = 1134), one study assessed 1224 patients who were exposed or not exposed to methylphenidate during different time periods (this study was also included among the cohort studies), 177 were cohort studies (n = 2,207,751), two were cross-sectional studies (n = 96), and 70 were patient reports (n = 206) (Figure 1).

Participants of all genders were included. Ages varied between three to 20 years, and the majority of studies were conducted in high-income countries. The duration of the studies lasted from one day to two years for comparative cohort studies, from one year to 11 years for patient-control studies, and from one day to ten years for cohort studies.

Correspondence emails were sent out twice to 174 authors, out of whom 109 answered. Many authors provided missing methodological and sociodemographic data, and some provided data on missing statistics.

Five comparative cohort studies/patient-control studies were found to be at serious risk of bias, and six other comparative cohort studies/patient-control studies to be at critical risk of bias. All other cohort studies and patient reports were regarded as having critical risk of bias due to lack of control groups.

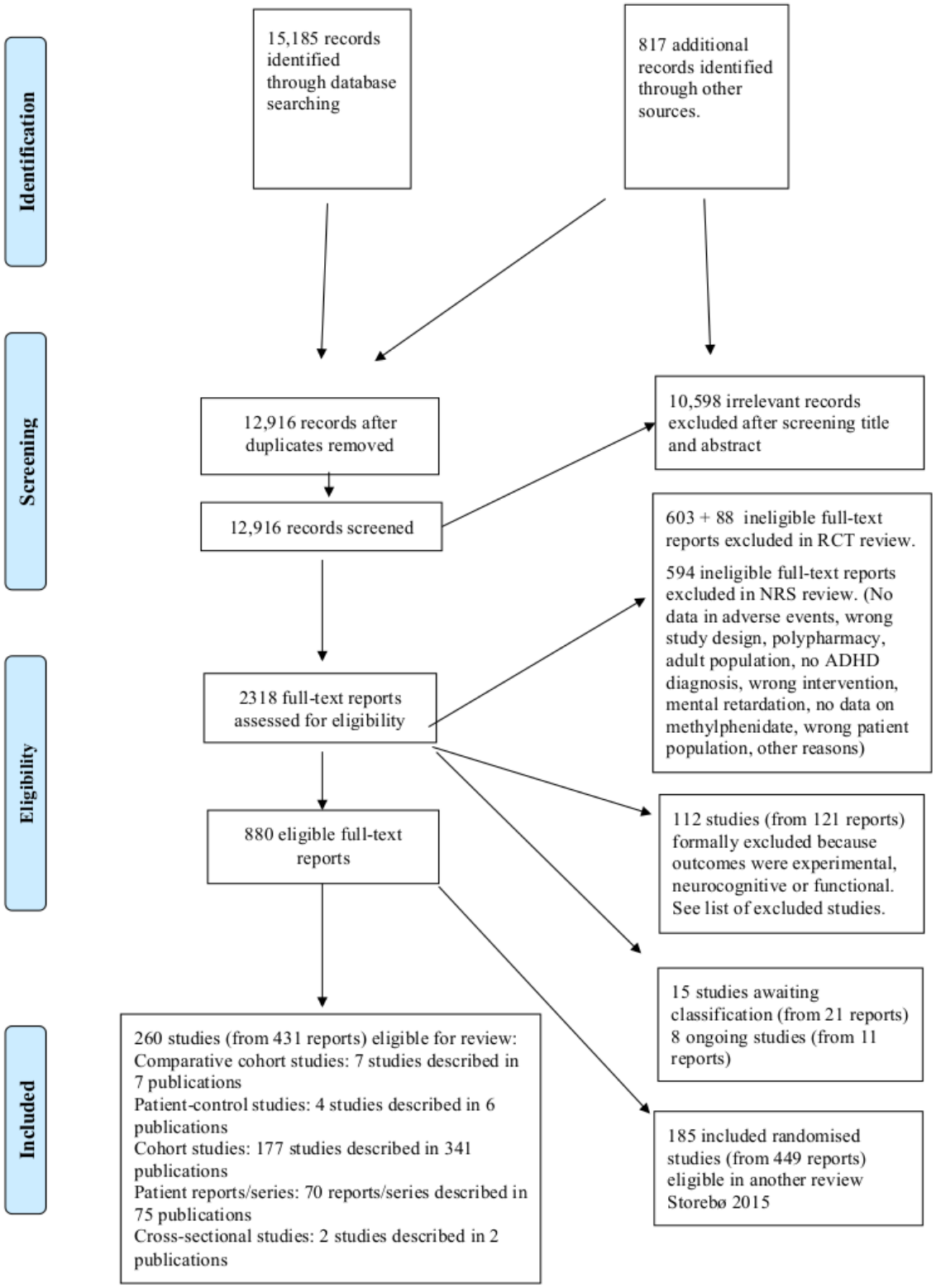

Figure 5. PRISMA flowchart. (The figure is reprinted from Storebø 2018 with the permission from publisher Wiley).

6.1.5 Primary outcome: serious adverse events

In comparative cohort and patient-control studies, the risk ratio of any serious adverse event in methylphenidate-exposed patients compared to those not given methylphenidate was (RR 1.36, 95% CI 1.17 to 1.57, 2 studies, 72,005 participants). In a patient-control study, the risk ratio for a psychotic disorder in methylphenidate-exposed patients was (RR 1.36, 95% CI 1.17 to 1.57, 1 study, 71,771 participants) compared to those not given methylphenidate.

In non-comparative cohort studies, the proportions of patients on methylphenidate with suicide attempts was 2.10 % (proportion 95% CI 0.40 % to 9.00 %; 3 studies, 339 participants), the proportions of patients who withdrew from methylphenidate treatment due to serious adverse events was 1.20 % (95% CI 0.60% to 2.30%, 7 studies, 1173 participants) and the proportion of patients on methylphenidate with any serious adverse event was 1.20 % (95 % CI 0.70% to 2.00 %, 50 studies, 162,422 participants). The most commonly reported serious adverse events were sudden death (0.20 %), suicide (0.10%), suicide attempt (2.10%), psychotic symptoms (1.20%), and severe depression (1.20%).

The numbers may be higher, as about 5% to 10% had their treatment withdrawn due to adverse events of unknown seriousness (see below).

6.1.6 Secondary outcome: non-serious adverse events

In the non-comparative cohort studies, the proportion of patients who withdrew from methylphenidate treatment due to adverse events of unknown severity was 7.30% (95% CI 5.30% to 10.0%; 22 studies, 3708 participants) and the proportions of patients on methylphenidate with non-serious adverse events was 51.2% (95% CI 41.2 % to 61.1%, 49 studies, 13,978 participants).
The proportion of patients on methylphenidate with decreased appetite was 31.1 % (95% CI 26.5% to 36.2%, 84 studies, 11,594 participants) and the proportion of patients on methylphenidate with abdominal pain was 10.7 % (95% CI 8.60% to 13.3%, 79 studies, 11,750 participants).

Across non-comparative cohort studies, the most commonly reported non-serious adverse events were decreased appetite, sleep difficulties, anxiety, irritability, and sadness.

6.2 Discussion

This is the first systematic review of non-randomized studies on short and long-term adverse events from methylphenidate treatment in children and adolescents with ADHD. Only two out of eleven comparative cohort studies and patient-control studies reported on serious adverse events, yet with results showing an increase in serious adverse events in the methylphenidate-exposed groups. In correlation, evidence synthesis from non-comparative cohort studies also showed higher rates of serious adverse events in patients treated with methylphenidate. Patient reports of serious adverse events included psychosis, hepatic reactions, and cardiovascular events. Non-serious adverse events linked to methylphenidate included headache, sleep difficulties, abdominal pain, and decreased appetite.

The proportion of patients who withdrew from methylphenidate treatment due to serious adverse events and adverse events of unknown seriousness were elevated in non-comparative cohort studies. Because many studies did not provide details of the specific adverse events that led to withdrawal, the true rate of serious adverse events may actually be higher than what our findings currently indicate.

6.3 Rates of adverse events

Our review reveals higher rates of a range of adverse events than what has been reported elsewhere (70). Guidelines on the use of methylphenidate in children and adolescents with ADHD should be updated to reflect these new data. Our previous Cochrane review (2) found smaller or similar proportions of adverse events compared to the present review, although only a small number of the included randomised clinical trials reported on non-serious adverse events. We compared the proportion of adverse events in the present review (Table 1) with the proportions in our published systematic review on methylphenidate versus placebo or no intervention (2), and national summaries of product characteristics (116-118). Compared to the other sources of data, we here found a higher proportion of adverse events on most symptoms in the present review.

Adverse event	Randomised clinical trials: methylphenidate group (from Storebø 2015)	Randomised clinical trials: placebo or no intervention group (from Storebø 2015)	National Summary of Product Characteristics (UK, USA, DK)	Non-comparative cohort studies and cohort studies from randomised trials (present review)	Non-comparative cohort studies (present review)	Non-comparative cohort studies from randomised trials (present review)
Serious adverse events	1.90% (95% CI 1.10% to 3.20%; 9 studies, 919 participants)	2.80% (95% CI 1.70% to 4.80%; 9 studies, 613 participants)	No information	1.20% (95% CI 0.70% to 2.00%; 51 studies, 162,434 participants)	1.10% (95% CI 0.60% to 2.00%; 32 studies, 159,761 participants)	1.60% (95% CI 1.00% to 2.30%; 18 studies, 2661 participants)
Non-serious adverse events	51.4% (95% CI 41.9% to 60.9%; 21 studies, 1861 participants)	38.3% (95% CI 30.3% to 47.0%; 21 studies, 1271 participants)	No information	51.2% (95% CI 41.2% to 61.1%; 49 studies, 13,978 participants)	47.1% (95% CI 35.6% to 58.9%; 36 studies, 13,035 participants)	62.1% (95% CI 44.4% to 77.1%; 13 studies, 943 participants)
Headache	11.6% (95% CI 8.80% to 13.3%; 17 studies, 1642 participants)	9.40% (95% CI 7.10% to 12.4%; 17 studies, 1082 participants)	1% to 10%	14.4% (95% CI 11.3% to 18.3%; 90 studies, 13,469 participants)[a]	9.90% (95% CI 7.00% to 13.9%; 57 studies, 10,929 participants)	24.3% (95% CI 18.0% to 32.1%; 33 studies, 2540 participants)
Anxiety	6.50% (95% CI 1.20% to 29.2%; 3 studies, 356 participants)	12.4% (95% CI 8.30% to 18.0%; 3 studies, 240 participants)	1% to 10% (UK and DK); no information (USA)	18.4% (95% CI 11.3% to 28.7%; 22 studies, 1287 participants)[a]	10.2% (95% CI 5.30% to 18.9%; 8 studies, 938 participants)	27.9% (95% CI 17.8% to 40.8%; 14 studies, 349 participants
Sleep difficulty	8.00% (95% CI 5.80% to 11.1%; 13 studies, 1417 participants)	8.30% (95% CI 6.40% to 10.7%; 13 studies, 999 participants)	1% to 10%	17.9% (95% CI 14.7% to 21.6%; 82 studies, 11,507 participants)[a]	14.3% (95% CI 11.2% to 18.2%; 51 studies, 9073 participants)	25.4% (95% CI 18.2% to 34.4%, 31 studies, 2434 participants)
Irritability	6.40% (95% CI 3.70% to 10.8%; 11 studies, 1038 participants)	3.50% (95% CI 1.40% to 8.60%; 11 studies, 778 participants)	1% to 10%	17.2% (95% CI 11.5% to 25%; 35 studies, 4792 participants)[a]	15.5% (95% CI 10.2% to 22.7%; 21 studies, 3298 participants)	20.6% (95% CI 7.90% to 44.1%; 14 studies, 1494 participants)
Tics	2.30% (95% CI 1.00% to	5.50% (95% CI 3.70% to	No information	6.40% (95% CI 4.50% to	5.60% (95% CI 3.80% to	10.6% (95% CI 5.30% to

	5.20%; 7 studies, 684 participants)	8.10%; 7 studies, 476 participants)		8.90%; 39 studies, 1980 participants)[a]	8.10%; 29 studies, 1601 participants)	19.9%; 10 studies, 379 participants)
Drowsiness	7.30% (95% CI 2.40% to 20.2%; 4 studies, 510 participants)	6.70% (95% CI 2.60% to 16.2%; 4 studies, 310 participants)	1% to 10%	9.50% (95% CI 5.20% to 16.6%; 17 studies, 1146 participants)[a]	7.50% (95% CI 3.10% to 17.2%; 7 studies, 644 participants)	11.3% (95% CI 5.00% to 23.3%; 10 studies, 502 participants)
Sadness	5.70% (95% CI 1.30% to 21.9%; 4 studies, 382 participants)	4.20% (95% CI 0.90% to 16.9%; 4 studies, 318 participants)	No information	16.8% (95% CI 9.40% to 28.3%; 21 studies, 1802 participants)[a]	13.1% (95% CI 6.60% to 24.1%; 9 studies, 626 participants)	20.6% (95% CI 8.10% to 43.1%; 12 studies, 1176 participants)
Fatigue	4.80% (95% CI 2.30% to 9.90%; 6 studies, 471 participants)	6.50% (95% CI 4.30% to 9.60%; 6 studies, 387 participants)	1% to 10%	5.70% (95% CI 3.00% to 10.4%; 17 studies, 2182 participants)	5.60% (95% CI 2.80% to 10.9%; 5 studies, 673 participants)	7.80% (95% CI 5.80% to 10.5%; 12 studies, 1509 participants)
Abdominal pain	11.5% (95% CI 7.70% to 16.8%; 13 studies, 1406 participants)	7.60% (95% CI 5.00% to 11.5%; 13 studies, 935 participants)	0% to 10%	10.7% (95% CI 8.60% to 13.3%; 79 studies, 11,750 participants)[a]	7.60% (95% CI 5.70% to 10.0%; 46 studies, 9229 participants)	16.3% (95% CI 11.6% to 22.4%; 33 studies, 2521 participants)
Decreased appetite	17.3 (95% CI 12.3% to 24.2%; 16 studies, 1751 participants)	4.30% (95% CI 2.40% to 7.40%; 16 studies, 1211 participants)	1% to 10%	31.1% (95% CI 26.5% to 36.2%; 84 studies, 11,594 participants)[a]	28.8% (95% CI 23.0% to 33.5%; 57 studies, 9662 participants)	39.7% (95% CI 27.0% to 54.0%; 27 studies, 1967 participants)
Vomiting	5.70% (95% CI 4.00% to 8.00%; 11 studies, 1140 participants)	5.10% (95% CI 3.5% to 7.4%; 11 studies, 776 participants)	1% to 10%	7.30% (95% CI 3.70% to 13.4%; 20 studies, 2731 participants)[a]	7.10% (95% CI 2.80% to 17.0%; 11 studies, 1528 participants)	7.20% (95% CI 3.30% to 15.1%; 9 studies, 1203 participants)
Nausea	7.50% (95% CI 6.10% to 9.30%; 11 studies, 1174 participants)	5.20% (95% CI 3.80% to 7.10%; 11 studies, 821 participants)	> 10%	7.60% (95% CI 5.30% to 10.6%; 41 studies, 5612 participants)[a]	8.00% (95% CI 7.00% to 9.10%; 22 studies, 3921 participants)	10.4% (95% CI 5.80% to 17.9%; 19 studies, 1691 participants)
Decreased weight	6.30% (95% CI 3.80% to	2.40% (95% CI 1.00% to	1% to 10%	8.70% (95% CI 4.80% to	6.60% (95% CI 3.10% to	16.6% (95% CI 8.70% to

	10.3%; 6 studies, 472 participants)	5.70%; 6 studies, 387 participants)		15.3%; 26 studies, 5182 participants)[a]	13.3%; 17 studies, 4855 participants)	30.6%; 9 studies, 327 participants)

Table 1. Data on adverse events from published systematic review on methylphenidate versus placebo or no intervention (2), National Summary of Product Characteristics, and from the present review (7, 117-119). (The table is reprinted from Storebø 2018 with the permission from publisher Wiley).

6.4 Limitations

Many of the included studies did not have comparator group or other data for comparisons, which makes it difficult to ascertain whether these adverse events are caused by methylphenidate, or whether they rather reflect a part of ADHD and the co-occurring conditions. For example, sleep disturbances, tics, low mood, and anxiety are all commonly found in children with ADHD. However, we did conduct several subgroup analyses on whether dosage of methylphenidate, concurrent-medication, comorbidity, duration, age, or study design affected estimates (7). Adverse events reported in observational studies did not seem to depend on dose, duration of methylphenidate administration, comorbidity, age of participants, or study design (non-serious adverse events) (7). Interestingly, we observed fewer adverse events in individuals who were taking additional medication at the same time as methylphenidate (concurrent-medication users) (7).

The findings of this review should be interpreted in the context of the low certainty and the methodological limitations when analyzing non-randomised studies. Therefore, our findings may likely be underestimations of the real number of adverse events. This is especially common in industry-funded trials (106). Fifty-three of the 177 non-comparative cohort studies included in our review were funded by pharmaceutical companies, 11 studies had authors with connections to pharmaceutical advisory boards, and 45 of the 177 studies did not report sources of funding. In addition, only a few studies used rating scales to assess adverse events, which nevertheless is considered a more reliable assessment method.

Despite the large number of studies, which included more than 2,200,000 children and adolescents, only a small number of serious adverse events are reported here. Considering the high proportion of withdrawals due to adverse events of unknown seriousness (n =3708), potentially there could have

been many more. It should be considered a limitation that we do not have data on the number of adverse events occurring at baseline. We were also not able to thoroughly assess the certainty of all the included non-comparative cohort studies. However, we assessed these studies as having critical risk of bias. It is important to understand that high risk of bias in randomised clinical trials has been shown to overestimate benefits and underestimate harms in such trials (2). Considering risk of bias in observational studies and reporting on harms, the risks are rather underreporting of harms.

6.5 Strengths

Non-randomised studies may in some cases be the only way to assess rare and serious adverse events (120). Ioannidis et al. state that many randomised clinical trials merely report the statistically significant results of harm exposure and that the studies are usually underpowered to detect differences in harms for severe events, as well as for the majority of rarely occurring and moderate events (121). This further underline the need for including non-randomised studies when assessing harms.

Our study is based on a highly comprehensive review: A protocol was published in accordance with The Cochrane Collaboration's guidelines with the literature search focusing broadly on both published and unpublished data. Data was analyzed using the Cochrane Handbook methodology and risk of bias was assessed using ROBINS-I (114). If studies lacked information on adverse events, we made great efforts to contact authors, and in some cases we managed to access further unpublished adverse events data. Although we still had to exclude many studies with missing data, we believe our review findings represent the highest achievable knowledge in this area at present.

7. The debate in the field and summary of evidence on the benefits and harms of methylphenidate for children and adolescents with ADHD from 2015 to 2019 (Papers 8 and 9).

Our two Cochrane systematic reviews (2, 7) have raised an intense debate in the field. This was especially the case with the first review published in 2015 (2) (see Table 2). Following this publication in 2015, there was an intense interest from the public media, with several newspapers and TV media covering the story concerning the lack of evidence for the use of methylphenidate

(*Ritalin use for ADHD "not trialed reliably". Research raises questions over ADHD drug effects*, The Daily Telegraph*; Experts call for caution over Ritalin*, Fox News (web); *Research raises questions over ADHD drug effects, BBC News*, Reuters (web); *More studies needed on ADHD drug Ritalin.* Sky News Australia (Web) and many more). Quickly the BMJ version of our review received comments criticizing different aspects of our review mostly regarding our assessment of certainty, risk of bias, and the need for nocebo trials (active placebo) which we subsequently responded to (58).

Table 2. Publications and comments focusing on the systematic review published in The Cochrane Library in 2015(2), with co-publications in The BMJ 2015(58) and The JAMA 2016(122)
Mulder R, Hazell P, Rucklidge JJ, Malhi GS. Methylphenidate for attention-deficit/hyperactivity disorder: too much of a good thing? Australian & New Zealand Journal of Psychiatry 2016;50(2):113–4. [DOI: 10.1177/0004867415626823] Available from anp.sagepub.com/search/results?fulltext=storebo&x=0&y=0&submit=yes&journal_set=spanp&src=selected&andorexactfulltext=and
Levy F. Methylphenidate for attention-deficit/ hyperactivity disorder: the longest debate. Australian & New Zealand Journal of Psychiatry 2016;50(7):616–7. [DOI: 10.1177/0004867416643390] Available from anp.sagepub.com/content/50/7/616.full.pdf
Hoekstra PJ, Buitelaar JK. Is the evidence base of methylphenidate for children and adolescents with attention-deficit/hyperactivity disorder flawed? European Child & Adolescent Psychiatry 2016;25(4):339–40. [DOI: 10.1007/s00787-016-0845-2] Available from link.springer.com/article/10.1007/s00787-016-0845-2
Storebø OJ, Simonsen E, Gluud C. The evidence base of methylphenidate for children and adolescents with attention-deficit hyperactivity disorder is in fact flawed. European Child & Adolescent Psychiatry 2016;25(9):1037–8. [DOI:10.1007/s00787-016-0855-0]. Available from link.springer.com/article/10.1007/s00787-016-0855-0
Banaschewski T, Gerlach M, Becker K, Holtmann M, Döpfner M, Romanos M. The errors and misinterpretations in the Cochrane analysis by O. J. Storebo and colleagues on the efficacy and safety of methylphenidate for the treatment of children and adolescents with ADHD. Trust, but verify. Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie 2016;44:307-14. [DOI: 10.1024/1422-4917/a000433] Available from econtent.hogrefe.com/doi/abs/10.1024/1422-4917/a000433
Storebø OJ, Zwi M, Moreira-Maia CR, Skoog M, Camilla G, Gillies D, et al. Response to "Trust, but verify" by Banaschewski et al. Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie 2016;44:334-5. [DOI: 10.1024/1422-4917/a000472]. Available from econtent.hogrefe.com/doi/abs/10.1024/1422-4917/a000472
Banaschewski T, Buitelaar J, Chui CSL, Coghill D, Cortese S, Simonoff E, et al. Methylphenidate for ADHD in children and adolescents: throwing the baby out with the bathwater. Evidence-Based Mental Health 2016;19(4):97-9. [DOI: 10.1136/eb-2016-102461] Available from ebmh.bmj.com/content/19/4/97.full

Storebø OJ, Zwi M, Krogh HB, Moreira-Maia CR, Holmskov M, Gillies D, et al. Evidence on methylphenidate in children and adolescents with ADHD is in fact of 'very low quality'. Evidence-Based Mental Health 2016;19(4):100-2. Available from ebmh.bmj.com/content/19/4/100.full
Vogt H, Lunde C. Drug treatment of ADHD-tenuous scientific basis. Tidsskrift for den Norske laegeforening: tidsskrift for praktisk medicin. 2018;138(2).
Storebo OJ, Faltinsen E, Zwi M, Simonsen E, Gluud C. The jury is still out on the benefits and harms of methylphenidate for children and adolescents with attention-deficit/hyperactivity disorder. Clin Pharmacol Ther. 2018;104(4):606-9.
Swanson JM. Risk of bias and quality of evidence for treatment of ADHD with stimulant medication. Clin Pharmacol Ther. 2018;104(4):638-43.
Comments to The Cochrane Library version of the review in The Cochrane Library(2)
None
Comments to The BMJ version of the review(58):
Fazel M. Methylphenidate for ADHD. BMJ 2015;351:h5875. [DOI: 10.1136/bmj.h5875]. Available from bmj.com/content/351/bmj.h5875.long
Grant E. Re: Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials [personal communication]. Response to: OJ Storebø, HB Krogh, E Ramstad, CR Moreira-Maia, M Holmskov, M Skoog, et al. 27 November 2015. Available from bmj.com/content/351/bmj.h5203/rr
Kremer HJ. Re: Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials [personal communication]. Response to: OJ Storebø, HB Krogh, E Ramstad, CR Moreira-Maia, M Holmskov, M Skoog, et al. 27 November 2015. Available from bmj.com/content/351/bmj.h5203/rr-0
Chandrasekaran V, Mahadevan S. Re: Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials [personal communication]. Response to: OJ Storebø, HB Krogh, E Ramstad, CR Moreira-Maia, M Holmskov, M Skoog, et al. 29 November 2015. Available from bmj.com/content/351/bmj.h5203/rr-1
Büchter RB, Thomas S. Re: Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials [personal communication]. Response to: OJ Storebø, HB Krogh, E Ramstad, CR Moreira-Maia, M Holmskov, M Skoog, et al. 10 December 2015. Available from bmj.com/content/351/bmj.h5203/rr-3
Saripanidis S. Management and treatment of hyperactivity and ADHD, without methylphenidate [personal communication]. Response to: OJ Storebø, HB Krogh, E Ramstad, CR Moreira-Maia, M Holmskov, M Skoog, et al. 27 December 2015. Available from bmj.com/content/351/bmj.h5203/rr-5
Banaschewski T, Buitelaar J, Chui CSL, Coghill D, Cortese S, Simonoff E, et al, on behalf of the European ADHD Guidelines Group. Are Methylphenidate Effects in Children with ADHD Really Uncertain? [personal communication]. Response to Storebø OJ, Krogh HB, Ramstad E, Moreira-Maia CR, Holmskov M, Skoog M, et al. 27 July 2016. Available from bmj.com/content/351/bmj.h5203/rr-6

Replies
Storebø OJ, Gluud C. Re: Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials [personal communication]. Response to: E Grant, HJ Kremer, V Chandrasekaran, S Mahadevan. 30 November 2015. Available from bmj.com/content/351/bmj.h5203/rr-2
Storebø OJ, Gluud C. Re: Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials [personal communication]. Response to: RB Büchter, S Thomas. 22 December 2015. Available from bmj.com/content/351/bmj.h5203/rr-4
Storebø OJ, Zwi M, Gluud C. Re: Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials [personal communication]. Response to: T Banaschewski, J Buitelaar, CSL Chui, D Coghill, S Cortese, E Simonoff, et al. 29 July 2016. Available from bmj.com/content/351/bmj.h5203/rr-9
Storebø OJ, Zwi M, Gluud C. Re: Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials [personal communication]. Response to: T Banaschewski, J Buitelaar, CSL Chui, D Coghill, S Cortese, E Simonoff. 29 July 2016. Available from bmj.com/content/351/bmj.h5203/rr-10
Storebø OJ, Zwi M, Gluud C. Re: Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials [personal communication]. Response to: T Banaschewski, J Buitelaar, CSL Chui, D Coghill, S Cortese, E Simonoff. 29 July 2016. Available from bmj.com/content/351/bmj.h5203/rr-11
Comments to The JAMA version of the review(122):
Shaw P. Quantifying the benefits and risks of methylphenidate as treatment for childhood attention-deficit/hyperactivity disorder. JAMA. 2016;315(18):1953-5. [DOI:10.1001/jama.2016.3427]. Available from jamanetwork.com/journals/jama/article-abstract/2520612
Romanos M, Reif A, Banaschewski T. Methylphenidate for attention-deficit/hyperactivity disorder. JAMA. 2016;316(9):994-5. [DOI:10.1001/jama.2016.10279]. Available from jamanetwork.com/journals/jama/article-abstract/2547744
Reply
Storebø OJ, Simonsen E, Gluud C. Methylphenidate for attention-deficit/hyperactivity disorder — Reply. JAMA. 2016;316(9):995. [DOI:10.1001/jama.2016.10300]. Available from jamanetwork.com/journals/jama/article-abstract/2547750

7.2 The blog by Chris Hollis

In March 2016, Chris Hollis posted a very critical blogpost on the Mental Elf webpage (https://www.nationalelfservice.net/mental-health/) named: *Methylphenidate for ADHD: have*

Cochrane got it wrong this time? (123). In summary Hollis wrote*: "The outcomes reported in this review show that* ***methylphenidate*** *is a* ***highly effective***, ***safe*** *and* ***generally well-tolerated*** *treatment for* ***ADHD****, with findings similar to those of previous meta-analyses. However, the idiosyncratic approach used by the authors for assessing quality of evidence deviates significantly from the standard Cochrane method and as a result, exaggerates the risk of bias assessment and excessively downgrades the quality of evidence."*

"Crucially, the authors themselves showed in the full Cochrane review (but did not report this in the BMJ paper) that ***'vested interests' bias did not materially affect the results****. Therefore, the author's interpretation of the results and conclusion that the '*strength of evidence is insufficient to guide practice*' is* ***misleading*** *and* ***potentially dangerous*** *as it could undermine the confidence of practitioners, children and parents in what is an effective and generally safe treatment".*

Chris Hollis is professor in Child and Adolescent Psychiatry and a former chair of the NICE guideline working group on ADHD in children and adolescents. We responded in detail to all the critical points raised by Hollis (123). The main critical point raised by Hollis was that we had assessed the certainty of the evidence erratically and that this was misleading and potentially dangerous as it could potentially undermine the confidence in the medication. In one of the many comments sent back and forth between Hollis and Christian Gluud and myself, Hollis referred to the Cochrane systematic review on methylphenidate treatment for adults with ADHD, which was published 18 September 2014. The conclusion of this review was, that "*Data from randomized controlled trials suggest that immediate-release methylphenidate is efficacious for treating adults with ADHD with symptoms of hyperactivity, impulsivity, and inattentiveness, and for improving their overall clinical condition. Trial data suggest that adverse effects from immediate-release methylphenidate for adults with ADHD are not of serious clinical significance, although this conclusion may be limited, certainly in the case of weight loss, by the short duration of published studies"* (124). Epstein et al. considered the certainty of the evidence rated by the GRADE instrument on most outcomes to be of high certainty: *For all outcomes except inattentiveness, the quality of evidence was assessed as "high" according to the GRADE approach. For the outcome of inattentiveness, most information was derived from studies judged to have unclear risk of bias; therefore, the quality of evidence for this outcome was judged as "moderate" in keeping with the GRADE approach"* (124). Hollis used this particular Cochrane review to argue that we had been

too strict when assessing the certainty of evidence. However, a closer look at the review by Epstein et al. revealed several methodological problems, and we therefore submitted critical comments concerning these methodological problems to the Cochrane group having the editorial responsibility on 10 May 2015 (125). Our main point of criticism was that the authors failed to adequately assess the certainty of the evidence, as the evidence was not downgraded for risk of bias, heterogeneity, or imprecision in the cases where it should have been. Following additional critical comments from other parties, the review by Epstein et al. was eventually withdrawn from The Cochrane library on 26 May 2016 with the following reason stated by Cochrane: ”*This review has been withdrawn from The Cochrane Library as of Issue 5, 2016. The authors have been unable to provide a satisfactory response to a number of criticisms received on the review. In addition, they contravene Cochrane's Commercial Sponsorship Policy. The editorial group responsible for this previously published document have withdrawn it from publication"* (126). We published an article in BMJ Evidence Based Medicine in 2017, describing our criticism of the review by Epstein et al., that we and others previously had submitted to Cochrane (127). Phillip Shaw stated in an editorial, which was published alongside a synopsis version of our review in JAMA (122), that the Epstein et al. review on methylphenidate for adults with ADHD was an example of good quality assessment (128).

7.3 The critical articles and letters from the EUNETHYDIS group

In 2016, Banaschewski et al. from The European Network for Hyperkinetic Disorders (EUNETHYDIS) published a critical article with the title: "The errors and misinterpretations in the Cochrane analysis by O. J. Storebø and colleagues on the efficacy and safety of methylphenidate for the treatment of children and adolescents with ADHD. Trust, but verify" in the German journal Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie (129). In this paper, they presented critical points concerning errors in the data, flawed study selection and erratic assessment of bias. They stated the following in the conclusion of their abstract: "*The systematic review thus contradicts all previous reviews and meta-analyses. We here detail various examples of errors, inconsistencies, and misinterpretations in the review which led to false results and inadequate conclusions. We demonstrate that the study selection is flawed and undertaken without sufficient scientific justification resulting in an underestimation of effect sizes, which, furthermore, are inadmissibly clinically interpreted. The methodology of the assessment of bias and quality is not objective and cannot be substantiated by the data. Cochrane reviews lay claim to a high scientific*

quality and substantial relevance for evidence-based clinical decisions. The systematic review by Storebo and colleagues (2015) illustrates that, despite adhering to strict standards and high-quality protocols, even Cochrane works should be critically read and verified, sometimes with surprising results".

We responded to this by publishing a "letter to editor" in the same journal, in which we wrote that our trial selection was not flawed and that our data collection and interpretation of data was systematic and sound. In addition, our assessment of quality and conclusion were not misleading. We agreed that minor errors were present in the review, yet we were still able in this corresponding article to show, that the effects were negligible and that these minor errors did not affect our conclusions (130). A critical editorial by Pieter J. Hoekstra and Jan K. Buitelaar was published in 2016 in their journal "European Journal of Child and Adolescent Psychiatry". The editors of this journal raised some of the same issues concerning our erratic assessment of certainty. They were critical of our concern that easily recognizable adverse effects of methylphenidate could spoil blinding. Therefore, it might have been possible for raters to know which treatment the children were receiving. We have been advocating for a solution to this problem, by which future trials optimally should use a 'nocebo' or active placebo control which mimics the non-therapeutic effects of an experimental intervention. They were also very critical of our point that trials funded by the industry or conducted by people with affiliations to the industry could give a risk for systematic errors (risk of bias). In the editorial the two editors wrote: "*The authors' ideology should strictly speaking lead to a new situation where medication research is conducted by researchers funded independently from industry by public funding bodies like medical research councils. Dreams are the backbone of reality, as the novelist James Salter wrote, but it does not need long thinking to conclude that public funding bodies will never allocate the budgets needed to implement such a new policy"* (131). We have been heavily criticized by many for stating that there might be a risk of bias, both when pharmaceutical companies fund trials and when the authors are affiliated with such companies. We wrote a letter to the editors of the European Journal of Child and Adolescent Psychiatry, in which we stated that the evidence for the use of methylphenidate in children and adolescents with ADHD is flawed. We advocated for including vested interest as a risk of bias domain and emphasized the need for active placebo-controlled trials (132).

In our comments and response articles on the topic of vested interest, we wrote that there were different views on this particular topic, but that we believed there indeed are problems associated

with industry-funded trials. In correlation, the AMSTAR tool for methodological certainty assessment of systematic reviews includes funding and conflicts of interest as a domain (http://amstar.ca/). Sponsorship and conflicts of interest may influence intervention effects on outcomes, which have been showed by Andreas Lund and colleagues (106). There may also be many other ways by which involvement of the industry potentially leads to biased results in trials. These are not necessarily covered through the well accepted bias domains, e.g. through 'creative' and selective statistical analyses and through spinning (133-137).

Many other articles and letters have repeated similar criticism regarding our certainty assessment, including our use of the vested interest risk of bias domain, concerns that blinding may be affected by easily recognizable adverse events, and concerns that we erratically included too many non-eligible trials (such as crossover trials and trials with add-on treatment to methylphenidate). This criticism was often written by the same authors, most of them affiliated with the EUNETHYDIS organization (138, 139). We carefully considered and responded to all the criticism in a paper in BMJ Evidence Based Medicines (8), and in a letter to the editor in The JAMA(140).

7.4 Positive critics

Other articles commenting our review were more positive and supportive of our statements. One of these was the article published in the Australian & New Zealand Journal of Psychiatry by Mulder et al. (141). In the article the authors wrote: "*Of note, the MTA authors are now more circumspect, reporting that the initial advantages for optimally medicated participants had halved 10 months later and disappeared a year after this. This pattern of initial superiority of medication-based treatment that tapered and then evaporated has continued across all subsequent years of follow-up. The MTA authors now state that medication may not be an extended hoped for panacea and that a 'reconsideration' of the MTA findings may be necessary (Hinshaw et al., 2015). This and the new review by Storebø and colleagues should make us reflect again on the benefits versus risks of prescribing methylphenidate for children with ADHD. While the evidence base appears large, the quality of evidence is poor. Importantly, the evidence base is only for short-term use of methylphenidate and suggests, at best, a modest effect. The low quality of evidence means we remain uncertain of the reliability of the estimates of treatment benefit. In addition, methylphenidate is associated with increased risks of adverse events, and these events are likely to be underestimated".*

Furthermore, Lunde and Vogt published an article in the Journal for the Norwegian Medical Association where they wrote: "*Recent systematic reviews reveal a weak evidence base for the use of methylphenidate and amphetamines in the treatment of children and adolescents with an ADHD diagnosis. This should have implications for the follow up and understanding of these patients*" (142).

7.5 Constructive suggestion for new directions in the field (Paper 9)

We published an article in 2018 in the US journal Clinical Pharmacology & Therapeutics to try to sum up our research on methylphenidate as well as the evidence in the field (9). James Swanson who is one of the founders of the large Canadian/US ADHD trial: the Multimodal ADHD trial (the MTA trial) wrote a long article commenting on this article (143). He concluded that there was a need for new directions in the field and he suggested that instead of continuing to disagree and debate, it might be more productive to use the Cochrane reviews to identify agreements about serious problems in the ADHD field. He stated that long-term trials are needed and he suggest that the debate instead could be directed on how to conduct more long-term studies. In addition, he advocated for the need of consistency when assessing and reporting harms, and that there often is an under-reporting of harm in randomised trials. He also emphasized that the discussion of risk of bias due to vested interest is an important one and that there is a need for trials being conducted by investigators, who do not have vested interests. Regarding the discussion about the GRADE assessment evaluating the certainty of evidence, Swanson wrote: "*Guyatt et al described unresolved controversy about the quality of evidence in another field where "… discrepant judgements between intelligent and well-informed [investigators remained, and] even after direct contact and discussion, each group adhered to its own position", which is similar to the impasse of the debate related to the ADHD field. Also, Movsisyan et al described challenges associated with downgrading of the "best evidence possible", which is similar to the topics of the critiques in Table 2, and they suggested an extension of GRADE to address this" (143).*

7.6 Observational studies

Some observational studies have shown that the use of stimulants may have a preventive effect on the risk of injuries and criminality in people with ADHD. A Swedish national register study, including 25,656 participants, showed that treatment with medications for ADHD led to a 32% and

41% reduction in criminality among men and woman, respectively (144). In a large cohort of 710,120 individuals, of which 4557 individuals were diagnosed with ADHD before age 10, the use of methylphenidate was found to reduce emergency department visits by 46% and injuries by 44% (145). In a observational study by Chang et al., the researchers found that ADHD was associated with an increase in serious transport accidents and that sufficient treatment with ADHD medication reduced this risk by approximately 58%, especially in male patients (146). There have also been reports showing a reduction in motor vehicle crashes when patients were treated with methylphenidate (147). However, these studies are all non-randomised, and therefore the studies contain risk of bias of beneficial effects due to confounding factors, random errors or other errors. Furthermore, since there is a lack of sufficiently powered and well-conducted randomised clinical trials, it remains unclear, whether the abovementioned results constitute real benefits or rather statistical artefacts (58, 148).

Another concern is whether ADHD medication treatment may lead to substance abuse. However, this notion has been challenged by Chang and colleagues, who showed that on the contrary, prescription of ADHD stimulants were associated with a 31% decrease in substance abuse (149). A similar concern involves the association between ADHD treatment and suicide. Conflicting results also exist on this matter, as treatment subsequently has been correlated with a protective effect against suicide (150). In 1996, the NIMH (National Institute of Mental Health) funded a large multisite randomized clinical trial (the MTA trial) investigating the effect of ADHD medication in children aged 7-9 years with ADHD (of which approximately 97% received methylphenidate). The children were randomly assigned to four different treatment regimens: a) medication alone, b) behavioral treatment alone, c) combination of medication and behavioral treatment, or d) community treatment. After 14 months of treatment, results showed that combined treatment as well as medication alone both were clinically and statistically superior in reducing symptoms as compared with behavioral treatment alone and with the control group (The MTA Cooperative Group 1999) (151). This trial was a large (with 579 participants) and, in many ways, a very well designed and conducted trial. However, it also had its limitations, as there was no sufficient blinding of participants, personnel, or outcome assessors. This may potentially pose the risk of type 1 error, which subsequently may lower the certainty of the evidence. The results received intensive attention and led to substantial increase in medical treatment of ADHD from the year 1999 and onwards. The trial continued as an observational study for a further 14 years, which resulted in

several publications (152-154). A key finding from these studies was that it was no longer possible to detect any benefits of medication compared to behavioral treatment after prolonged follow-up. The latest follow-up article from the MTA group reported that there were no differences in symptoms rates, when investigating those receiving consistent medical treatment for the whole period compared to those with an inconsistent use of medication. Other subgroup analyses showed that there was a clear difference in physical height in the group that consistently received medication for 16 years as compared to the group that inconsistently received medication. As such, the group with consistent use of medication was 2.36 ± 1.13 cm shorter than the group with an inconsistent use of medication ($P < .04$, $d = .38$) (154).

In a recent study, the authors investigated whether a history of stimulant treatment could predict long-term improvement of ADHD core symptoms, social–emotional functioning or cognition, when measured after a medication washout period. During the trial period, one group received stimulant medical treatment and one group received no medical treatment. In addition, a control group with healthy controls was included. The degree of ADHD cores symptoms was evaluated at the beginning of the study and at a 6-year follow-up. The groups were matched on clinical and socio-demographic variables. In total, there were 148 participants included with an average age of 11.1 years.

The results showed no difference in the efficacy measures examined, between the group receiving medication and those not receiving medication. The researchers concluded that treatment with ADHD medication was not associated with improvement of ADHD core symptoms, socio-emotional functioning or working memory after a treatment period of six years (155).

7.7 Placebo discontinuation-trials

In a new placebo discontinuation-trial including ninety-four children and adolescents with ADHD Matthijssen et al. found beneficial effects of methylphenidate (156). The patients were randomly assigned to double-blind continuation of treatment for seven weeks or to gradual withdrawal over three to five weeks of placebo (156). Before start of the trial the children and adolescents had been treated in regular care with methylphenidate for more than two years. The primary outcome was the clinician rated ADHD Rating Scale (ADHD-RS). Secondary outcome was Clinical Global Impressions Improvement scale (CGI-I). The mean difference in change over time was -4.6 (95%

CI -8.7 to -0.56) on the ADHD-RS. The CGI-I indicated worsening in 40.4 % of the discontinuation group, compared with 15.9% of the continuation group. This trial states that long-term methylphenidate use is effective, however, a closer look at the ADHD-RS change show that this difference is not above the minimal clinical relevant difference (MIREDIF) of ADHD-RS of -6.6 points (89). We wonder if some of the worsening symptoms in the methylphenidate group could be withdrawal symptoms? It can be difficult to separate impression of recurrence of ADHD symptoms from occurrence of withdrawal symptoms from having an addicting drug removed. The placebo-withdrawal trial consists of a starting phase where patients who are openly treated with the medication are evaluated. In the second phase, participants who have responded well to medication are randomly assigned to continue the same treatment or switch to placebo. Those who show adverse reactions to methylphenidate are excluded from such trials. We therefore believe that the placebo withdrawal trials are not very well suited to estimate the magnitude of absolute treatment effects as they do it in a select group of patients (157).

7.8 The latest evidence

7.8.1 Reviews from 2015 to 2019

We previously conducted a search for systematic reviews, which included randomised clinical trials investigating the beneficial and harmful effects of methylphenidate use for children and adolescents with ADHD in PubMed, BMJ Best Practice, and The Cochrane Library. The search revealed several new reviews on the topic. One of these is the study by Catalá-López et al., who published a large systematic review with a network meta-analyses in 2017. They included 190 randomised clinical trials with a total of 26,114 children and adolescents with ADHD. They found that stimulant monotherapy was significantly more efficacious than placebo; however, all analyses were assessed in GRADE low or very low certainty. In addition, they found that stimulants increased the risk of anorexia (OR 8.01, 95% credibility limits (CrL) 5.75 to 11.34), weight loss (OR 21.64, 95% Crl 11.92 to 42.28) and sleep disturbance (OR 6.02, 95% Crl 2.81 to 14.45). In their conclusion, Catalá-López et al. stated that stimulants may improve the symptoms of ADHD especially when combined with behavioral treatment, yet the certainty of the evidence underlying these results is not very strong. They also state that there is an urgent need for high-certainty randomised trials of both pharmacological and behavioral treatments for ADHD in children and adolescents (158).

Another network meta-analyses published in 2018 by Padilha et al. (159) investigated the benefits and harms of different types of ADHD medications (including methylphenidate) for children and adolescents with ADHD. They included forty-eight trials with 4169 participants. The review found that there were beneficial effects of methylphenidate on the Clinical Global Impressions Improvement scale (CGI-I) and that methylphenidate was more effective than both the use of non-stimulant atomoxetine and guanfacine. The study found that methylphenidate had a worse safety profile as compared to other pharmaceutical treatments for ADHD, such as atomoxetine, bupropion, dexamphetamine, lixdexamfetamine, guanfacine, edivoxetine, of which a special concern was made towards the occurrence of adverse events, such as sleep disturbances and loss of appetite following treatment with methylphenidate. In contradiction to the review by Catalá-López et al., Padilha et al. assessed the methodological certainty of included trials as overall good, and reported that the studies were well designed, conducted and reported (159). There are several methodological problems with the review by Padilha et al., and therefore we submitted a critical letter (160). Our criticism focused on selection bias as the authors had excluded placebo controlled trials, they had an erroneous assessment of the certainty of the evidence and they did not include an overall assessment of certainty like the Grading of Recommendation Assessment, Development and Evaluation (GRADE) system. They also used the Jadad scale for the risk of bias assessment (161), despite this scale being outdated as well as lacking the crucial bias domain 'allocation concealment'. Furthermore, they included crossover trials without reporting the method on how to pool these trials with parallel-group trials, or discussing the possible issues such as carry-over and period effects (160). A network meta-analysis (NMA) consists of indirect and direct comparisons. The indirect comparisons in a NMA is based on a fundamental assumption of transitivity. The transitivity has the assumption that the studies included in the indirect comparisons must be sufficiently similar in all different aspects, apart from the treatments they compare. Padilha and colleagues did not assess the transitivity assumption in their network meta-analyses (162).

In August 2018, a large network meta-analysis and review was published by Cortese et al. (163) on medical treatment of ADHD in children, adolescents and adults. This review included 133 RCTs and evaluated the tolerability and efficacy of drug-treatment. The review concluded that there is good evidence for the use of methylphenidate in children/adolescents, and that this should be the first pharmacological choice for ADHD - in a treatment-period of 12 weeks. The authors of this network meta-analysis subsequently wrote that their findings are in line with the NICE guidelines (163). This review received intense media coverage in many newspapers and other media including

television. Professor and advisor for the NICE ADHD work group (and also co-author of this review) Emily Simonoff claimed in the newspaper The Guardian on August 7 2018: “The problem in the UK is predominantly about undermedication and underdiagnosis”.

In a critical letter published in The Lancet (164), we discussed the findings presented in this review by Cortese et al. We found it to be a comprehensive and very well conducted review, however, following a closer look several problems were revealed, as the authors hardly discussed the lack of data concerning the use of methylphenidate for more than 12 weeks and how this potentially should affect clinical practice. In addition, this review only assessed a few selective adverse events and since it is not reported which types of adverse events led to withdrawal, the severity of the reported harm measures on tolerability and acceptability is challenging to interpret. As such, data on additional serious and non-serious adverse events would have been informative for readers. Furthermore, the exclusion of potentially valuable studies (in order to limit the risk of bias) combined with the statistical and methodological assumptions made in this review might have increased the risk of selection bias (164). In a response to our critical letter, the authors admitted that they had excluded 65 % of the trials, which we previously had included in our review from 2015. They excluded 51 trials that had less than seven days of treatment, 38 crossover trials without a washout period and with no pre-crossover data, 18 trials with responders to previous treatment, and finally 14 trials where treatment was not monotherapy (165). They did this, because including these trials would have been a clear violation of their published protocol and would have compromised the transitivity of the network meta-analyses (165). In this way, they used the argument of fulfilling the transitivity assumption to defend the high selection bias. The transitivity assumption is about whether it was correspondingly likely that all the patients in the network analysis could have been given any of the treatments in the network.

Another review by Cerrillo-Urbina et al. was published in 2018 in Journal of Child and Adolescent Psychopharmacology (166). This review included 15 RCTs, with 4648 children and/or adolescents from 6 to 17 years of age diagnosed with ADHD. It investigated the benefits and harms of stimulant and non-stimulant medication. Only four trials included methylphenidate, all of which were conducted before 2013. They assessed potential bias using the Cochrane risk of bias tool and the GRADE instrument. The GRADE assessment of the evidence concerning the total score of ADHD symptoms was assessed to be of “moderately high evidence” for both stimulant and non-stimulant medications. They downgraded the evidence by one level due to high degree of heterogeneity in the

pooled results (I^2 > 75%), however they did not downgrade due to risk of bias or publication bias, even when they found that there was significant publication bias for all outcomes. It is striking that this review only included four trials on methylphenidate, as we found 185 trials in our review when searching the same period.

Another review published in 2017 by Joseph et al. investigated the benefits and harms of pharmacological treatment of children and adolescents 6 to17 years of age (167). A total of 36 randomised clinical trials were included in the review. When investigating the use of methylphenidate extended release, the mean difference on the ADHD-RS-IV total score change from baseline (medication compared with placebo) was −8.68 (−10.63 to −6.72). This is more than the MIREDIF of −6.6 points for the ADHD-RS-IV scale (89).

Data were unavailable for the use of methylphenidate immediate release. The review also found that lisdexamfetamine had a greater efficacy than guanfacine extended release, atomoxetine, and methylphenidate in the treatment of children and adolescents with ADHD. The authors of this review described that they used the NICE guideline method for certainty assessment (risk of bias) and that they assessed the included trials for randomisation procedure, allocation concealment, prognostics factors of groups, dropouts, outcome reporting bias, and method to handle missing data. The assessment of these domains is reported in a large table. They did not evaluate the risk of random errors in the analyses and did not downgrade due to imprecision and inconsistency. The risk of bias assessment was not used in any kind of overall assessment of certainty and it is not reported in connection with the certainty of the effect estimates (167).

A review by Li et al. (168) was published in 2017 with network meta-analyses, which found that methylphenidate was effective in the treatment of ADHD in children and adolescents. According to the authors of this review, lisdexamfetamine, methylphenidate, clonidine hydrochloride and guanfacine extended release all had a high efficacy in treating ADHD. Methylphenidate was considered the second most safe treatment compared to the other types of ADHD medications. The review included 62 trials in a meta-analysis, which included 12,930 patients. The review did not make any attempt to evaluate risk of bias or the certainty of evidence. This lowers the robustness and validation of this review (168).

Another new meta-analysis evaluated the risk of increased systolic blood pressure (SBP) and heart rate (HR) post vs. pre-treatment, when taking methylphenidate, placebo or atomoxetine. This meta-

analysis found that children/adolescents and adults treated with methylphenidate experienced a significant increase in heart rate and systolic blood pressure as compared to placebo (169). This review included 22 studies of different designs, 18 studies were randomized clinical trials, two studies were prospective cohort studies, and two studies were retrospective cohort studies. The review assessed the certainty of the included randomised clinical trials by using the outdated Jadad scale. In this meta-analysis, 16 out of 22 studies (72.7%) achieved the Jadad score ≥ 3, indicating good certainty. As mentioned, one substantial limitation to the Jadad scale is that it does not include an assessment of the allocation concealment procedure (161).

A systematic review by Liu et al. investigated the risk of cardiovascular diseases and found that there was no correlation between ADHD medications and sudden death/arrhythmia, stroke, myocardial infarction and all-cause death (170). However, when taking a closer look at the confidence intervals, some of these do not exclude a modest elevated risk, e.g., for sudden death/arrhythmia. The review included ten studies on children, adolescents and adults with ADHD (total 4,221,929 participants) (170).

Pozzi et al conducted a systematic review investigating adverse drug events during medical treatment of children with ADHD. The review included 45 trials on different types of medication, of which 36 trials included treatment with methylphenidate. The review did not assess the certainty of the included studies and had a limited search strategy, as only PubMed was searched. Overall, they concluded that methylphenidate might reduce symptoms of irritability and anxiety, as well as euphoria, but worsen the symptoms of apathy and reduce talkativeness (171).

7.8.2 Summary

In summary, we found nine reviews from 2015 to 2019, which were of varying quality and gave somewhat inconsistent conclusions. Although these studies all had several limitations (some serious), general findings includes support for methylphenidate might be an effective short-term first-line treatment for ADHD (158, 159, 163, 166-168), as well as some evidence that methylphenidate may produce higher risk for adverse events than placebo or non-stimulant ADHD medications (169-171).

8. International guidelines on methylphenidate for children and adolescents with ADHD (Paper 10)

8.1 The guidelines

There are several clinical guidelines worldwide concerning the management of ADHD. These include the National Institute for Health and Care Excellence (NICE) guideline which was updated in March 2018(172), the American Academy of Pediatrics (AAP) Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents which was updated in 2019 (173), the American Academy of Child and Adolescent Psychiatry (AACAP) (53), the German S3 guideline which was updated in 2017 (174), and the national clinical guideline on management of ADHD in children and adolescence from the Danish Health Authorities, which was updated in 2018 (119). In addition, there is a guideline specifically focusing on the management of adverse effects following ADHD medication published by the guidelines group of the European Network for Hyperkinetic Disorders (EUNETHYDIS) (70).

The NICE guideline recommends methylphenidate as the first-line pharmacological treatment for children over five and adolescents (1.7.7: *Offer methylphenidate (either short or long acting) as the first line pharmacological treatment for children aged 5 years and over and young people with ADHD*). The NICE guideline committee concludes that methylphenidate and lisdexamfetamine provide clinically important benefits to patients with ADHD as compared to placebo and other drugs (175). However, a closer look at the NICE guideline reveals several methodological problems, which especially involves an erroneous assessment of the certainty of the included studies. The certainty was assessed as high certainty, when it could be debated that the certainty in fact was low. In the assessment of the effect of methylphenidate, they only included 16 trials, which solely focused on immediate and osmotic-release methylphenidate in children and adolescents. We included 185 trials (of which 175 were placebo-controlled) in our review from 2015 (58). NICE did not adjust for multiple comparisons and they did not discuss the concern that all data was assessed during a short-term follow-up. Since ADHD is a chronic disease, the lack of long-term investigations must be considered a critical problem (176). As such, the strong clinical practice recommendation for the use of ADHD medication given in the NICE guideline is based on a foundation of studies with low certainty of evidence and short-term data. In addition, the guideline

itself includes serious methodological limitations, including selective reporting and inadequate adjustments for multiple comparisons (10).

In 2019, the recommendations provided by the American Academy of Pediatrics guideline were updated based on patient's age. In this guideline, the following age range was applied: 1) preschool-aged children: age four years to the sixth birthday; 2) elementary and middle school–aged children: age six years to the 12th birthday; and 3) adolescents: age 12 years to the 18th birthday. In regards to preschool-aged children, the guideline recommends evidence-based behavioral interventions (parent training in behavior management and/or behavioral classroom interventions) as the first-choice treatment. Methylphenidate may be considered if the child has moderate to severe problems with functioning and if the behavioral treatment does not provide the necessary improvements. In regards to schoolchildren, the guideline strongly recommends pharmaceutical treatments (US Food and Drug Administration (FDA)–approved medications for ADHD) together with the above evidence-based behavioral interventions. Regarding adolescents the guideline strongly recommends pharmaceutical treatment and if possible, evidence-based behavioral interventions. Educational interventions and individualized instructional support are also recommended. The guideline states that there is a strong effect observed in the trials investigating the effects of stimulant medications (173). The risk of harm is considered as low and the benefits in general are described as outweighing the risks. This guideline does not refer to our two Cochrane reviews investigating the beneficial and harmful effects of methylphenidate for children and adolescents.

The German S3 guideline (161) recommends methylphenidate treatment for children and adolescents with ADHD. They use our review from 2015 and refer to the effect sizes obtained from our data analyses (2). The conclusion in our review is the following: "*The results of meta-analyses suggest that methylphenidate may improve teacher-reported ADHD symptoms, teacher-reported general behavior, and parent-reported quality of life among children and adolescents diagnosed with ADHD. However, the low quality of the underpinning evidence means that we cannot be certain of the magnitude of the effects*" (2). The German guideline, however, fails to mention our concerns regarding the low quality of evidence and the impact it may have on the effect size (174). The Danish guideline (119) makes use of both our reviews as the main body of evidence for their recommendations concerning the use of methylphenidate for children and adolescents (2, 7). They recommend a psychosocial or behavioral treatment as the first line treatment for children and adolescents with ADHD. This is the case for both children with mild ADHD displaying better

functioning as well as for children with more severe ADHD and lower level of functioning. In regards to administration of methylphenidate, the guideline provides a strong recommendation for its use in children with severe ADHD and low level of functioning. Only a weak recommendation is given for the use of methylphenidate in children with mild ADHD and better functioning (119). The guideline produced by the guidelines group of the European Network for Hyperkinetic Disorders (EUNETHYDIS) concludes that some of the adverse effects examined appear to be difficult to distinguish from the risk found in untreated populations, and that some of the adverse events may have a minimal impact on the patients. Nevertheless, they do underline that further studies are needed to determine the risk of adverse events (70).

8.2 WHO model list of essential medicines

The WHO Model List of Essential Medicines serves as guidance for the development of national and institutional essential medicine lists. This list is updated and revised every two years by the WHO Expert Committee on Selection and Use of Medicines. In December 2018 the WHO Model List of Essential Medicines received an application from Patricia Moscibrodzki and Craig L. Katz (177). The application consisted of arguments for including methylphenidate on the list. The application was based on a systematic review investigating the use, efficacy, safety, availability, and cost-effectiveness of methylphenidate for children, adolescents and adults with ADHD as compared with other stimulant (first-line) and non-stimulant (second-line) medications. The application stated that methylphenidate consistently proves to be superior in regards to efficacy and tolerability, and with only few reported adverse effects. The application did not include an assessment of the certainty of the evidence (177). Nevertheless, the application was backed up by several recommendation letters.

We were worried about the trustworthiness of some parts of the application, as we found important limitations in the way the evidence was reported (177). We submitted our concerns in a public comment published on the WHO webpage (178). Our critical comments mainly focused on the certainty of evidence, the short duration of the individual trials, a misplacement of evidence, and a strong suspicion of strategic use of selective bias. In the application, they referred to our Cochrane systematic review published in 2015, and reported the observed methylphenidate effect sizes in children and adolescents with ADHD (178). This however, was without mentioning any of our concerns about the certainty of the evidence. This deliberate failure to mention important

information concerning the evidence is similar to how the updated German SL3 guideline used our review data (174).

The WHO Model List of Essential Medicines Expert Committee decided to reject the application, based on the following: "*The Expert Committee did not recommend the addition of methylphenidate to the complementary list of the Essential Medicine List (EML) and Essential Medicine List children (EMLc) for the treatment of attention-deficit hyperactivity disorder (ADHD) due to concerns regarding the quality and interpretation of the evidence for benefits and harms*"((179) 26, page 314). The decision made by the committee was unanimous.

9. General discussion

Since methylphenidate has been used for more than 60 years as a treatment for ADHD, we considered it essential that the evidence concerning the use of this medication was thoroughly investigated. Following a search for relevant literature, we found 15 systematic reviews published between 2002 and 2014. A subsequent assessment of the individual reviews revealed several shortcomings that essentially could affect the results being reported. All of the identified reviews had methodological limitations. Of essential notice, none of them was based on a pre-published protocol. Accordingly, none of the reviews were systematic reviews according to Cochrane (86). Several of the reviews failed to evaluate the risks of bias in the trials that they had included and none of the reviews assessed the risks of random errors. Most reviews did not assess the number of adverse events associated with the medication. Due to these limitations, we believe that intervention effect estimates and subsequent conclusions reported in these reviews are questionable and unfairly prejudiced. All of the reviews report on high effect sizes for methylphenidate compared with placebo, without taking into account the methodological limitations found in each individual trial (risks of bias), the poor reporting of adverse events, and the problems with combining small trials in meta-analyses. As such, they erroneous overlook the uncertainty in the analysis. This is problematic, given that there has been an increase in the use of medication for children and adolescents with ADHD, especially within the last twenty years. In order to understand today's medication practices, it is essential to go back to the MTA trial, which was published in 1999. The MTA trial showed that after 14 months of treatment, administration of medication combined with behavioral treatment as well as medication alone led to better clinical outcomes, than when only

behavioral or community treatment were applied. This large MTA trial together with the abovementioned 15 systematic reviews have been the reason for the enormous increase in the use of methylphenidate for ADHD in children and adolescents. This despite the fact that the MTA trial had methodological limitation due to the lack of blinding and that all the later follow-up time point in the MTA trial showed, that the beneficial effect of methylphenidate declined over time (152-154). Our Cochrane systematic review published in 2015 (2) came as a surprise to the world of psychiatrists, psychologists, and other professionals as well as ADHD patients and their families. We were questioning the well-known 'truth' of methylphenidate being a very effective treatment for children and adolescents with ADHD and the 'fact' that the adverse events were manageable and unproblematic (70). In our review from 2015, we found that methylphenidate seems to reduce ADHD core symptoms as well as improve quality of life and general behavior, but also that the GRADE certainty in the effect estimates is very low. We also found that at a first glance there seems to be no serious adverse events associated with methylphenidate, however, when looking closer, it became evident that this was difficult to fully assess due to lack of data. Furthermore, we found that there was an increased risk for a number of non-serious adverse events such as decreased appetite and sleep problems. Our results raised an intense debate, with the publication of many articles and letters to editors, which all especially criticized our quality assessment of the included trials and our use of the vested interest domain. This domain is not always used in the Cochrane risk of bias tool, but we think it should be included under risk of publication bias in GRADE (180). We agree that this should be assessed as a separate domain, as there might be a substantial risk of bias regarding conflict of interests, when pharmaceutical companies are involved in trials and when authors are affiliated with the industry. This only means that there would be further reason to downgrade the certainty of the evidence. Our assessment of this domain in the Cochrane risk of bias tool did not influence our overall assessment of the risk of bias in the trials. There would still have been a high risk of bias, even if we had dealt with vested interest bias under publication bias.

One other aspect of our review, which was heavily criticized, was our comments regarding the need for 'nocebo' or 'active placebo' trials. We stated that methylphenidate could affect blinding in the experimental group, due to several easily recognizable adverse events observed during methylphenidate treatment, by which it might be possible for participants to decipher which treatment the children were receiving. In a similar vein, the placebo treated group would not sense anything, also leading to deblinding in this group. These methodological limitations may explain

some of - or all of - the observed small beneficial effects. We wrote that a solution of this problem would be to use a 'nocebo' or 'active placebo' control, which mimics the non-therapeutic effects of an experimental intervention. The response was that this was an impossible requirement, which could not be done. We are now planning a large project (the Active placebo control interventions in randomised clinical drug trials - methylphenidate for ADHD (APORT-m study)), which includes several PhDs and post-doctoral projects to investigate the issue of active placebo use in depth. The APORT-m study is based on the overall concern that experimental drug interventions in randomised clinical trials may unblind participants and personnel due to noticeable psychotropic or adverse effects. We are planning to systematically review active placebo control interventions in randomised clinical drug trials in children and adults, by comparing effects of active placebo versus standard placebo (meta-analysis of trials randomising to both, and meta-epidemiological study of meta-analyses of trials using either). In addition, we will develop procedures for rationally choosing between different candidates for active placebos as well as conduct a pilot randomised clinical trial of methylphenidate versus active placebo and versus standard placebo for ADHD in adults (181). If methylphenidate appears better than active placebo in adults, then later similar trials may be considered for adolescents and then children.

Because of the potential for benefit and the limited data on adverse events, we published another Cochrane systematic review based on non-randomised studies, in which we made use of various forms of observation data, including patient reported data (7). This review included data from 260 empirical studies with 2,283,509 patients.

This review revealed that there might be a risk of serious adverse events. In the comparative studies, methylphenidate increased the risk ratio (RR) of serious adverse events (RR 1.36, 95 % confidence interval (CI) 1.17 to 1.57, 2 studies, 72,005 participants); any psychotic disorder (RR 1.36, 95 % CI 1.17 to 1.57, 1 study, 71,771 participants); and arrhythmia (RR 1.61, 95 % CI 1.48 to 1.74; 1 study, 1224 participants) compared to no intervention. In the non-comparative cohort studies, the proportion of participants on methylphenidate experiencing any serious adverse event was 1.20 % (95 % CI 0.70 % to 2.00 %, 50 studies, 162,422 participants). Withdrawal from methylphenidate due to any serious adverse events occurred in 1.20 % (95 % CI 0.60 % to 2.30 %, 7 studies, 1173 participants) and adverse events of unknown severity led to withdrawal in 7.30 % of participants (95 % CI 5.30 % to 10.0 %, 22 studies, 3708 participants). Moreover, more than 50 % of the participants had at least one non-serious adverse event. In the comparative studies,

methylphenidate, compared to no intervention, increased the RR of insomnia and sleep problems (RR 2.58, 95 % CI 1.24 to 5.34, 3 studies, 425 participants) and decreased appetite (RR 15.06, 95 % CI 2.12 to 106.83,1 study, 335 participants). With non-comparative cohort studies, the proportion of participants on methylphenidate with any non-serious adverse events was 51.2 % (95 % CI 41.2 % to 61.1 %, 49 studies, 13,978 participants). These included difficulty falling asleep, 17.9 % (95 % CI 14.7 % to 21.6 %, 82 studies, 11,507 participants); headache, 14.4 % (95 % CI 11.3 % to 18.3 %, 90 studies, 13,469 participants); abdominal pain, 10.7 % (95 % CI 8.60 % to 13.3 %, 79 studies, 11,750 participants); and decreased appetite, 31.1 % (95 % CI 26.5 % to 36.2 %, 84 studies, 11,594 participants). Withdrawal of methylphenidate due to non-serious adverse events occurred in 6.20 % (95 % CI 4.80 % to 7.90 %, 37 studies, 7142 participants), and 16.2 % were withdrawn for unknown reasons (95 % CI 13.0 % to 19.9 %, 57 studies, 8340 participants). (This section is copied from the abstract of the review with the permission from publisher Wiley).

This latter review received surprisingly little attention in comparison to our 2015 review. However, we were invited to publish an overview article of the two reviews in the US journal Clinical Pharmacology and Therapeutics (9). One of the coordinating investigators of the MTA trial, James Swanson, wrote an article in the same journal commenting on our 2015 and 2018 reviews. He wrote that we had given a precise summary of our reviews and he suggested that the field now had to find a way to move forward from the continuous debate that had been ongoing since the publication of our reviews. Swanson suggested that it might be more productive to identify agreements on serious problems within the ADHD field. One of these was the lack of long-term trials. In a pro-con article published in JAACAP in June 2019 (Debate: Are Stimulant Medications for Attention-Deficit/Hyperactivity Disorder Effective in the Long Term?), Swanson wrote that the evidence documents a short-term effectiveness, but that studies also show that the effect may diminish over time. He made use of both trial and observational data, as well as patterns of medication used in clinical practice, to show that patients eventually stop using medication and that data shows that there seems to be a pharmacological and neural adaptation to stimulants (182). David Coghill was the other debater in this article and he argued that there is evidence showing long-term benefits of stimulant medication. Coghill admitted that there is a lack of randomised clinical trials with longer duration, yet he argues that it is possible to use the randomised withdrawal designs to demonstrate the benefits of stimulant medication over a period of six to 12 months. He wrote that several of these trials have been published and that they all show continued effect of the medication. There is a need to get this literature systematically reviewed and to try to assess what is ‘continued effect’ and

what is occurrence of abstinence symptoms. Furthermore, Coghill points at several new register studies, which all show a long-term protective effects of stimulants (183). The randomised discontinuation trial consists of two phases: in phase one all patients who are openly treated with the medication are evaluated. In the second phase, only those who have responded to medication are randomly assigned to continue the same treatment or switch to placebo. Those who show adverse reactions are excluded from phase two. We believe that the placebo discontinuation trials are not very well suited to estimate the magnitude of absolute treatment effects (157). The register studies are also problematic when the goal is to assess the benefits of treatment, since they are at high risk of bias due to confounding factors (184). In his article in Clinical Pharmacology and Therapeutics, Swanson also underlined the need for consistency when assessing and reporting adverse events in clinical trials, and he acknowledged that there often is an underreporting of adverse events. Furthermore, Swanson agreed with us, that there is a need for more trials to be conducted by investigators without vested interests. Finally, Swanson underlined the need for consistency in the use of the GRADE tool and perhaps better guideline to support the correct assessment of uncertainty of evidence (143). When assessing the observational data, we found data supporting that stimulants and methylphenidate might have a protective effect on the risk for injuries, traffic accidents, and mortality, however, as pointed out earlier, there is a risk for overlooking confounding factors in these studies (184).

In regards to effect estimates, the newer reviews published from 2015 to 2019 showed a somewhat contradicting picture, as two large network meta-analyses differed in their assessment of the certainty of evidence. Cortese et al. (163) found the evidence to be of moderate quality and therefore they were more confident in the evidence as compared with Catalá-López et al. (158). Cortese assessed very few adverse events and found that the overall tolerability of methylphenidate was good. This was in contrast to Catalá-López et al. who found an extremely high risk for anorexia, weight loss, and sleep disturbance during treatment.

An article by Wong et al. was published on behalf of the European ADHD Guidelines Group, in which an overview of the pharmacotherapy research on ADHD was presented. The authors described that despite an enormous research effort, there are several gaps in the knowledge base, and several questions concerning the quality of evidence exist. The issues concern the uncertainties of long-term evidence and safety as well as the comparative effectiveness of different medications.

It is interesting to read that this group now recognizes the problems with the evidence base (185). However, it is striking to see that they do not cite our research even when we were one of the first to give attention to the problem of the quality of evidence and the problem with long-term safety. The group of authors describes, that the solution to these problems is to increase the use of randomised placebo-controlled withdrawal trials and large pharmacoepidemiological studies that use electronic health-care records to investigate the long-term effectiveness and safety of medications. Furthermore, there is the need for more pragmatic head-to-head randomised clinical trials to find the direct evidence on comparative effectiveness and safety profiles. As mentioned, we do not agree with this, as we believe that placebo discontinuation studies are not very well suited to estimate the magnitude of absolute treatment effects (157) and that the register studies are also problematic when assessing benefits of treatments as there is a high risk of bias due to confounding factors (184). We recognize that the large register studies might be valuable, especially if they are conducted well and planned in a way that takes into account the risk of confounding factors.

Surprisingly, the latest large NICE guideline only included 16 trials to evaluate the effect of methylphenidate (172). The certainty of evidence was considered high, which we believe is an erroneous assessment as we found the certainty of evidence to be low or very low. The updated American Academy of Pediatrics guideline stated that there is a strong effect observed in the trials investigating the effects of stimulant medications (173) and that the risk for adverse events is considered low. This guideline does not refer to our two Cochrane reviews investigating the beneficial and harmful effects of methylphenidate for children and adolescents. The German guideline does refer to our reviews and they completely ignore the aspect concerning the certainty of the evidence (174). The Danish guideline makes use of both our reviews as their main body of evidence for the recommendations concerning the use of methylphenidate for children and adolescents (119). They give only a weak recommendation for the use of methylphenidate in children with mild ADHD and better functioning. This guideline seems to use our data in a fashion that is more in line with our interpretation (119).
The application for including methylphenidate to The WHO Model List of Essential Medicines was rejected, due to the concerns regarding the quality of the evidence for benefits and harms in children, adolescents and adults with ADHD (177, 179). The decision made by the committee was unanimous. One could argue that the evidence sent to the committee was not complete, when one compared with the total evidence published within the field. However, even if the application had

included more evidence, the result would most likely have been the same. The European Guideline Group also states in their overview article published in Lancet Psychiatry in 2019, that despite enormous research efforts in the field there are several gaps in the knowledge base and several questions concerning the quality of evidence exist (185). In a seminar article published in The Lancet February 2020, the authors gave an overview of the pharmaceutical treatment for ADHD in children and adolescents. The authors of the article wrote that there was strong evidence supporting a short treatment effect of methylphenidate. They did not report anything concerning the quality of the evidence and instead took for granted what had previously been reported. The authors wrote that there were several concerns with stimulant medications, as most studies showed that the use of stimulant medication over several years could affect growth trajectories, and they report that there is evidence showing, that there are doubts on whether treatment effects persists in the long term. The authors state, that it is important to develop new treatments that takes into account the research focusing on the causes and nature of ADHD as well as to develop new treatment options that are tailored to fit the patients individual needs (186).

10. Future directions

ADHD is considered by many to be a chronic disorder and it is very often being treated medically for several years. It is uncertain whether the possible short-term effect of medical treatment persists over time, and whether termination of medical treatment results in a deterioration of functioning. There is a need for well-powered, methodologically rigorous randomised clinical trials that focus on both benefits and harms. It is important to secure blinding (e.g. use of an 'active placebo'), to publish a priori protocols that reduce publication bias, and to take actions towards reducing vested interests. In clinical practice it is important to establish a clear baseline concerning comorbid conditions, which should include a thorough cardiovascular history and examination, recording of sleep and eating patterns, and a systematic assessment of family history of other risk factors. It is also vital to employ structured monitoring systems, using appropriate instruments to record adverse events over time. When prescribing methylphenidate treatment, clinicians need to carefully balance the risks of adverse events against the potential benefit for each individual patient. Clinicians should share and help with interpreting the available evidence, to facilitate informed clinical decision-making together with the children and adolescents receiving treatment, as well as their parents. The upcoming trials should publish anonymous individual participant data and report all outcomes,

including adverse events. This will enable researchers to conduct better systematic reviews that assess differences between intervention effects according to sex, age, type of ADHD, presence of comorbidities, and dose. The new systematic reviews should use all the available tools to objectively assess the quality of the trials and thereby the certainty of the evidence. They should objectively discuss and use the latest version of overall quality tools such as the GRADE. Finally, there is also an urgent need for large randomised clinical trials of non-pharmacological treatments (187).

11. Summary

The aim of this thesis was to assess the beneficial and harmful effects of methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). ADHD is a commonly diagnosed and treated childhood neurodevelopmental disorder and it is estimated to affect 3 to 8% of children and adolescents.

Methylphenidate has been used for more than 60 years as a treatment for ADHD and it is one of the most prescribed drugs for ADHD. Methylphenidate appears to have a positive effect in reducing the core symptoms of ADHD in children and adolescents, with fifteen systematic reviews published between 2002 and 2014 showing that methylphenidate is beneficial and with few harms. However, a subsequent assessment of the individual reviews revealed several methodological shortcomings that essentially could affect the results reported in the identified reviews. These methodological limitations may explain some of or all of the observed small beneficial effects. In our Cochrane systematic review of randomised clinical trials from 2015, we found that methylphenidate versus placebo or no intervention seems to reduce ADHD core symptoms as well as improve quality of life and general behavior, but also that the Grading of Recommendations Assessment, Development and Evaluation (GRADE) certainty in the effect estimates was very low. We also found that there seems to be no obvious serious adverse events associated with methylphenidate, although there is an uncertainty connected to this finding, due to lack of data and inadequate reporting. Furthermore, we found that there was an increased risk in the number of non-serious adverse events when treated with methylphenidate.

Our results raised an intense debate with publication of several articles and letters to editors, which all especially criticized our quality assessment of the included trials. In addition, we were criticized for our statement, that methylphenidate could affect blinding in the experimental group, due to occurrence of several easy recognizable adverse events during methylphenidate treatment. As such, we stated that it might be possible for participants to decipher which treatment the children were receiving. We responded to these criticisms in several corresponding articles and letters, in which we once again showed that the evidence was uncertain due to several methodological limitations.

Because of the potential for uncertain benefits and limited data on adverse events, we published yet another Cochrane systematic review based on non-randomised studies, in which we made use of various types of observation data, including patient reported data. This review included 260 empirical studies with 2,283,509 patients. This review revealed that there might be a risk of serious adverse events and that more than 50% of all children had one or more types of adverse events. After we published an overview article of both reviews in Clinical Pharmacology and Therapeutics, some of our main critical points regarding the data on methylphenidate were recognized and it was suggested that the field has to find a way to move forward from the continuous debate. It was suggested that it might be productive to identify agreements on serious problems within the ADHD field.

One of these problems includes the lack of long-term trials. At the same time, others suggested the need for placebo discontinuation trials and the need of long-term register based studies in order to identify long-term evidence. We do not agree with this, as we believe that placebo discontinuation studies are not well suited to estimate the magnitude of absolute treatment effects and also that register studies are problematic when assessing benefits of treatments, as there is a high risk of bias due to confounding factors. We do however recognize that the large register studies might be valuable, especially if they are conducted well and planned in a way that takes into account the risk of confounding factors.

Newer reviews published from 2015 to 2019 showed a somewhat contradicting picture, as two large network meta-analyses differed in their assessment of the certainty of evidence. One found that the evidence was of moderate quality and therefore the authors were more confident in the evidence as compared with another review who found that the certainty of the evidence was uncertain.

In an article published on behalf of the European ADHD Guidelines Group, the authors described that despite an enormous research effort, there are several gaps in the knowledge base and that several questions concerning the quality of evidence still exist. These issues concerns the uncertainty of the long-term evidence and safety as well as the comparative effectiveness of different medications. It is interesting to read that this group now recognizes the problems with the evidence base.

Surprisingly, the latest large NICE guideline only includes few trials to evaluate the effect of methylphenidate. The certainty of evidence was considered high, which we believe is an incorrect assessment, as we found the certainty of evidence to be low or very low. The updated American Academy of Pediatrics guideline stated that there is a strong effect observed in the trials investigating the use of stimulant medications and that the risk for adverse events is considered low. This guideline does not refer to our two Cochrane reviews investigating the beneficial and harmful effects of methylphenidate for children and adolescents. The German guideline refers to our reviews, yet without including our main concern regarding the certainty of the evidence and thus the uncertainty regarding the magnitude of the genuine treatment effect. The Danish guideline makes use of both our reviews as the main body of evidence in their recommendations concerning the use of methylphenidate for children and adolescents. They only provide a weak recommendation for the use of methylphenidate in children with mild ADHD and better functioning. This guideline seems to use our data in a fashion that is more in line with our interpretation.

The application for including methylphenidate to the WHO Model List of Essential Medicines was rejected due to the concerns regarding the quality of the evidence supporting the benefits and harms in children, adolescents and adults with ADHD. One could argue that the evidence sent to the committee was incomplete, when one compared this with the total evidence published within the field. However, even if the application had included more evidence, the result would most likely have been the same. ADHD is considered by many to be a chronic disorder and it is very often treated medically for several years. It is uncertain whether the possible short-term effect of medical treatment persists over time, and whether termination of medical treatment results in a deterioration of function. There is a need for well-powered, methodologically rigorous trials that focus on both benefits and harms. It is important to secure blinding (e.g. use of an ‘active placebo’), to publish a

priori protocols that reduce publication bias, and to take actions towards reducing vested interests. When prescribing methylphenidate treatment, clinicians need to carefully balance the risks of adverse events against the potential benefit for each individual patient.

12. Dansk resumé

Denne afhandlings formål var at undersøge de gavnlige og skadelige effekter af behandling med methylphenidat til børn og unge med attention deficit hyperactivity disorder (ADHD). ADHD er en hyppigt diagnosticeret og behandlet udviklingsforstyrrelse hos børn, og det anslås at 3% til 8% af børn og unge har diagnosen ADHD. Methylphenidat er blevet brugt i mere end 60 år som en behandling af ADHD og er anset som et af de mest anvendte lægemidler mod ADHD sammenlignet med andre medikamenter. Methylphenidat kan have en positiv indvirkning på de kernesymptomer, der observeres hos børn og unge med ADHD. Tilsvarende har femten review publiceret imellem 2002 og 2014 vist, at methylphenidat har gavnlige effekter og få skadevirkninger. Ikke desto mindre har vores gennemgang af disse review afsløret flere metodemæssige problemer, som tilsammen har kunnet påvirke de rapporterede resultater.

I vores Cochrane review af randomiserede kliniske forsøg fra 2015 fandt vi, at methylphenidat ser ud til at reducere ADHD-kernesymptomer samt forbedre livskvaliteten og generel adfærd, men at vi samtidig fandt frem til at tiltroen til estimaterne, vurderet ud fra GRADE metoden, var meget lav. Vi fandt også, at der ikke synes at være nogen umiddelbart alvorlige bivirkninger forbundet med brugen af methylphenidat, men at dette er usikkert på grund af manglende data og ufuldstændig rapportering. Desuden fandt vi, at der var en øget risiko for en række ikke-alvorlige bivirkninger forbundet med brugen af methylphenidat.

Vores resultater i det første Cochrane review har rejst en intens debat, og det har medført, at en række artikler og 'editorials' er blevet publiceret i kølvandet på vores review, hvor alle især kritiserer vores kvalitetsvurdering af de inkluderede forsøg samt beskrivelse af, at methylphenidat potentielt kan påvirke blindingen i et forsøg grundet adskillige let genkendelige bivirkninger. Vi vurderer således, at det på baggrund af disse genkendelige bivirkninger bliver muligt for forældre og pårørende at finde frem til, hvilken behandling børnene har modtaget i forsøget. Den kritik, der er kommet frem på baggrund af vores review, har vi efterfølgende afvist i flere artikler og 'letters to

editor', hvor vi ligeledes samtidig påviser, at evidensen er usikker på grund af adskillige metodologiske begrænsninger. På baggrund af de begrænsede data vedrørende skadelige virkninger, publicerede vi i 2018 et Cochrane review baseret på ikke-randomiserede studier. Dette review inkluderede 260 studier med i alt 2.283.509 patienter, og det viste, at der kan være en risiko for alvorlige bivirkninger, samt at over 50% af alle børn, der modtog methylphenidat havde en eller flere typer bivirkninger. Efter offentliggørelse i Clinical Pharmacology and Therapeutics af en oversigtsartikel, der beskrev begge review, blev nogle af vores vigtigste kritikpunkter anerkendt, og det blev antydet, at feltet nu burde finde en måde til at komme videre fra den lidt fastlåste debat. Det blev beskrevet, at det kunne være produktivt at identificere de problemområder, som der er konsensus omkring, i forhold til evidensen for behandling af børn og unge med ADHD med methylphenidat. Et af disse problemområder omhandler manglen på randomiserede kliniske forsøg, som på lang sigt måler både virkningen samt forekomsten af skadelige effekter af methylphenidat. Derudover blev det påpeget, at langtidseffekterne kunne undersøges i såkaldte 'placebo withdrawal studier' og via langvarige registerbaserede undersøgelser. Vi er ikke enige i dette, da vi mener, at 'placebo withdrawal studier' ikke er velegnede til at estimere absolutte behandlingseffekter, og også at registerundersøgelserne er problematiske på grund af høj risiko for confounding faktorer. De store registerundersøgelser kan dog være værdifuld forskning, især hvis de udføres godt, og hvis det er planlagt på en måde, der tager højde for netop risikoen for confounding faktorer.

I henhold til den manglende konsensus omkring kvaliteten af evidensen, viste to nyere review publiceret fra 2015 til 2019 et noget modstridende billede. Således fandt ét review, at evidensen var af moderat kvalitet, hvorfor teamet af forfattere var mere sikre på resultaterne sammenlignet med et andet review, der vurderede at evidensen var usikker.

I en artikel offentliggjort på vegne af den europæiske ADHD guideline gruppe beskrev forfatterne, at der til trods for en enorm forskningsindsats er adskillige mangler i vidensgrundlaget på området. I en opdaterede retningslinje fra NICE vedrørende ADHD, var der kun få forsøg inkluderet i evalueringen af effekten for methylphenidat. Evidensen blev betragtet som værende af høj kvalitet, og der var forholdsvis stor tiltro til resultaterne. Vi mener, at dette er en fejlagtig vurdering, da retningslinjen fra NICE udelader mange forsøg, hvilket potentielt kan fordreje billedet i forhold til effekten af behandlingen. Den opdaterede retningslinje fra American Academy of Pediatrics beskrev, at der er fundet god effekt af methylphenidat, og at risikoen for bivirkninger anses for at

være lav. Denne retningslinje henviser ikke til vores to Cochrane review. Den tyske retningslinje henviser til vores review, men vælger at ignorere vores primære anke imod evidensen, nemlig at den er usikker grundet den lave kvalitet af de inkluderede studier. Den danske retningslinje bruger begge vores Cochrane review som grundlag for anbefalingerne vedrørende brugen af methylphenidat til børn og unge. De giver kun en svag anbefaling i forhold til anvendelsen af methylphenidat til børn med let ADHD. Denne retningslinje ser ud til at bruge vores data på en måde, der er mere i overensstemmelse med vores fortolkning.

Ansøgningen om at optage methylphenidat på 'WHO's List of Essentiel Medicines' blev blandt andet afvist på grund af den lave kvalitet af evidensen, der understøtter methylphenidat som behandling til unge og voksne med ADHD. Man kunne hævde, at de data, der blev sendt til udvalget, ikke var komplette, når man sammenligner med al forskning på området, men selv hvis ansøgningen havde inkluderet flere studier, ville konklusionen sandsynligvis have været den samme.
ADHD betragtes af mange som værende en kronisk lidelse, og det behandles ligeledes meget ofte med medicin i flere år. Det er usikkert, om den mulige kortvarige effekt af medicinsk behandling fortsætter over tid, og om der givetvis vil fremkomme skadelige virkninger over tid. Der er behov for metodisk veludførte forsøg, der fokuserer på både de gavnlige og skadelige effekter. Det er vigtigt at sikre blinding (fx ved brug af 'aktiv placebo'), og at publicere a priori-protokoller, der giver metodologisk transparens, og som derved kan reducere publikationsbias. Ved ordinering af behandling med methylphenidat skal klinikere nøje afveje risikoen for bivirkninger imod den potentielle fordel for hver enkelt patient.

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