UNIVERSITY OF COPENHAGEN
FACULTY OF HEALTH AND MEDICAL SCIENCES

PhD Thesis

Methodological limitations of psychiatric drug trials

With a particular focus on extended-release methylphenidate

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This thesis has been submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen 21 July 2020

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Title	Methodological limitations of psychiatric drug trials with a particular focus on extended-release methylphenidate
Dansk titel	Metodebegrænsninger i psykiatriske lægemiddelforsøg med et særligt fokus på methylphenidat depotpræparater
Topic description	This thesis investigates the methodological limitations of psychiatric drug trials in four papers: (1) a systematic review of extended-release methylphenidate for attention deficit hyperactivity disorder in adults; (2) a reanalysis of a systematic review of antidepressants for depression in adults; (3) a cross-sectional study of EMA and FDA research guidelines for pivotal psychiatric drug trials; (4) a cross-sectional study whether methylphenidate formulations for adult ADHD were approved on select samples of clinical trials.
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“What has happened inside of me has not left any clear traces.
I saw something which disgusted me, but I no longer know whether it was the sea or the stone.
The stone was flat and dry, especially on one side, damp and muddy on the other.
I held it by the edges with my fingers wide apart so as not to get them dirty”

^

“Now I see: I recall better what I felt the other day at the seashore when I held the pebble.
It was a sort of sweetish sickness. How unpleasant it was!
It came from the stone, I'm sure of it, it passed from the stone to my hand.
Yes, that's it, that's just it - a sort of nausea in the hands”

Jean-Paul Sartre, Nausea (1938)

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Preface

This thesis and the included papers were conducted at the Nordic Cochrane Centre over two periods; from August 2015 to June 2016 and from November 2017 to July 2020. As part of my PhD, I visited the Unit of Innovation and Organization in Pamplona, Spain, in August 2018, and I spent six months at the Meta-Research Innovation Center at Stanford (METRICS), Stanford University, from September 2019 to February 2020. I did two of my PhD courses at the Department of Continuing Education, Oxford University, United Kingdom, in June 2019.

This thesis is a synopsis based on four papers:

1) **Boesen K**, Paludan-Müller AS, Gøtzsche PC, Jørgensen KJ. Extended-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults: Systematic review with meta-analyses of published and unpublished data. *Submitted* 2020.

2) Munkholm K, Paludan-Müller AS, **Boesen K**. Considering the methodological limitations in the evidence base of antidepressants for depression: a reanalysis of a network meta-analysis. *BMJ Open* 2019; 9:e024886. http://dx.doi.org/10.1136/bmjopen-2018-024886.

3) **Boesen K**, Gøtzsche PC, Ioannidis JPA. EMA and FDA psychiatric drug trial guidelines: Assessment of guideline development and trial design recommendations. *Submitted* 2020.

4) **Boesen K**, Jørgensen KJ, Gøtzsche PC. How many clinical trials are missing when drug regulators make decisions? A case study of extended-release methylphenidate for ADHD in adults. *Submitted* 2020.

The thesis is supported by the following publications:

Original research

1) **Boesen K**, Saiz LC, Erviti J, Storebø OJ, Gluud C, Gøtzsche PC, Jørgensen KJ. The Cochrane collaboration withdraws a review on methylphenidate for adults with attention deficit hyperactivity disorder. *Evid Based Med* 2017;22:143-7. http://dx.doi.org/10.1136/ebmed-2017-110716.

Protocols

2) **Boesen K**, Danborg PB, Gøtzsche PC, Jørgensen KJ. Extended-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults. *Cochrane Syst Rev* 2017;11:CD012857. https://doi.org/10.1002/14651858.CD012857.

3) **Boesen K**, Gøtzsche PC, Ioannidis JPA. FDA and EMA clinical research guidelines: Assessment of trial design recommendations for pivotal psychiatric drug trials (Protocol). *medRxiv 2020; 27 Jan.* https://doi.org/10.1101/2020.01.22.20018499.

Letters

4) **Boesen K**, Paludan-Müller, Munkholm K. Network meta-analysis of antidepressants. *Lancet* 2018;392:1011. https://doi.org/10.1016/S0140-6736(18)31783-5.

5) **Boesen K**, Gøtzsche PC. Quality of life of adult patients with attention-deficit/hyperactivity disorder taking methylphenidate. *JAMA Psychiatry* 2016;73: 533-4. https://doi.org/10.1001/jamapsychiatry.2016.0049.

Acknowledgements

I have imagined writing this section so many times, for such a long time, and now I am finally here. There are many people to thank, so please bear over with me.

First of all, I would like to thank Peter Gøtzsche for taking me under his wings, introducing me to medical research, and for having faith in me and giving me freedom and responsibility way too early. More importantly, I want to thank Peter for being a role model and mentor. I want to thank my colleagues at the Nordic Cochrane Centre, especially my co-supervisor, Karsten Juhl Jørgensen, for always being helpful, welcoming, meticulous and patient, especially during my time as a research rookie; Klaus Munkholm for being such an inspiration, enthusiastic and for listening to my monologues in his office; Asger Sand Paludan-Müller, my friend and roommate, whom I might never beat at Mario Kart, but who I can always count on. I'm gonna miss you by my side in Berlin; all other current and former colleagues at the office, and of course Jannie and Frihild for always being helpful. I also want to thank Jacob Rosenberg for stepping in and being a great help.

I want to thank my Spanish colleagues and good friends Juan Erviti and Luis Carlos Saiz from the Unit of Innovation and Organization for welcoming me in Pamplona. I also want to thank the METRICS team at Stanford, especially John Ioannidis for his tutorship, but also the rest of the team; Steve Goodman, Jack, Perrine, Janneke, Cathrine, Noah, Mario, Joel, Valentin and Stelios. What a team we were!

I want to thank Jannik Johansen for his mentorship and unlimited support; my Italian brothers, Luis, Taahir and Adam; my Spanish brothers/cani almas gemelas Paulino and Jose; my boys from the hood, Rune, Morten, Jonas and Niclas, and my friends from the remainder of my existence, Mads, Anders, Peter, Jannick, Asmus, Zeljko and Niclas for always being there.

I want to thank my family; my brother Lars and my shining star (and niece) Matilde.

Lastly, I want to thank my mom, dad, and my nephew Magnus. For always reminding me to never give up and for inspiring me to every day working harder.

Financial support

The Nordic Cochrane Centre funded this thesis.

For my stay at Stanford University, I received additional funding from the University of Copenhagen, Danmark-Amerika Fonden, Knud Højgaard Fonden and Augustinus fonden.

Conflicts of interest

None

Summary in English

It is critical for all drugs used in a healthcare setting that the benefits outweigh the harms; that clinical trials testing these drugs are designed to address patient relevant questions and that effect sizes are clinically relevant; and that new drugs are approved on the basis of all available evidence and not select samples of trials.

In this thesis, we assessed the benefits and harms of the central stimulant extended-release methylphenidate for use in adults with attention deficit hyperactivity disorder (ADHD) (*Paper 1*) and the methodological limitations of clinical trials with antidepressants for use in depression in adults (*Paper 2*). We investigated the European Medicines Agency (EMA) and the US Food and Drug Administration's (FDA) guidelines on how to design psychiatric drug trials that are used in new drug applications (*Paper 3*), and we assessed whether methylphenidate has been approved for use in adult ADHD based on all available clinical trials or select samples of trials (*Paper 4)*.

Paper 1: In our systematic review of extended-release methylphenidate for ADHD in adults, we included 25 randomised placebo-controlled trials (4,876 participants). We rated all trials at high risk of bias, and there were important limitations to the external validity. There were no effects of methylphenidate over placebo on 'days missed at work', whereas methylphenidate improved ADHD symptoms measured on rating scales and the effect on quality of life was negligible. Methylphenidate increased the risk of harm, including psychiatric harms. We judged the certainty of the evidence that benefits outweigh harms as "very low".

Paper 2: In our reanalysis of a systematic review of antidepressants for depression in adults, we assessed all 522 trials to as having unclear or high risk of bias. Trials using a "placebo lead-in" phase reported a larger effect size than trials without such a phase and unpublished trials reported a lower effect size compared to published trials. For a sample of trials, there were discrepancies in the reported data compared to available clinical study reports. We judged the certainty of the evidence that benefits outweighed harms to be "very low".

Paper 3: EMA and FDA publish guidelines on how to design pivotal psychiatric drug trials. The guideline development process is open to the public, but 80% of the involved stakeholders were from the industry or had financial conflicts of interest. The trial design

recommendations seemed to favour clinical trials with limited clinical and patient relevance, such as short duration, strict inclusion criteria, and surrogate outcomes.

Paper 4: We assessed publicly available regulatory documents related to twelve drug applications of extended-release methylphenidate for adult ADHD. We identified missing trials in seven of twelve documents, although current regulatory requirements seem to stipulate that all available evidence must be submitted for new drug applications.

In conclusion, the benefits and harms of extended-release methylphenidate for adult ADHD and antidepressants for depression in adults are uncertain due to methodological limitations in the clinical trials. Several of these methodological limitations, primarily related to the trials' generalisability, are recommended by EMA and FDA in their guidelines on how to design pivotal trials of psychiatric drugs. Finally, extended-release methylphenidate formulations have seemingly been approved based on a select sample of clinical trials.

Resume på dansk/ Summary in Danish

Det er essentielt, at lægemidler der bruges i sundhedsvæsenet har gavnlige virkninger som overstiger de skadelige; at kliniske lægemiddelforsøg er designet til at besvare klinisk relevante spørgsmål og lægemidlernes effektstørrelser har relevans for patienterne; og at nye lægemidler bliver godkendt på basis af alle tilgængelige kliniske forsøg og ikke kun et udvalg af forsøgene.

I denne afhandling har jeg forsøgt at afklare de gavnlige og skadelige effekter af depot-præparater af det centralstimulerende stof methylphenidat til behandling af ADHD hos voksne (*Artikel 1*) samt af antidepressiv medicin til behandling af voksne med depression (*Artikel 2*). Vi undersøgte de europæiske og amerikanske lægemiddelagenturers anbefalinger for design af kliniske forsøg af psykiatriske lægemidler (*Artikel 3*) og vi undersøgte om methylphenidat er blevet godkendt på baggrund af alle kliniske lægemiddelforsøg forsøg eller et udvalg af de tilgængelige forsøg (*Artikel 4*).

Artikel 1: I den systematiske oversigtsartikel om methylphenidat som depot-formulering for ADHD hos voksne inkluderede vi 25 forsøg med cirka 4,876 deltagere. Vi vurderede, at der for samtlige forsøg var høj risiko for bias og alvorlige begrænsninger ved deres generaliserbarhed. Vi fandt ingen effekt på tabt arbejdstid, methylphenidat forbedrede ADHD symptomer målt på symptomskalaer, og den gavnlige effekt på forbedret

livskvalitet var negligeabel. Præparaterne medførte mange skadelige virkninger, herunder psykiatriske skadevirkninger. Vores tiltro til evidensen var "meget lav".

Artikel 2: I vores reanalyse af en oversigtsartikel om antidepressiv medicin til voksne med depression, fandt vi at de kliniske forsøg havde usikker eller høj risiko for bias. Studier, der brugte en "indledende placebo-fase" rapporterede en større effekt end studier uden sådan fase, og det samme var gældende for offentliggjorte studier sammenlignet med ikke-offentliggjorte studier. Der var diskrepans mellem offentliggjorte data og forsøgenes rådata, og vores tiltro til evidensen var "meget lav".

Artikel 3: EMA og FDA udgiver retningslinjer for hvordan psykiatriske lægemiddelforsøg skal designes. Udviklingen af retningslinjerne er åben for alle, men 80% af de involverede interessenter kom fra industrien eller havde finansielle interessekonflikter. Myndighedernes anbefalinger favoriserer design af lægemiddelforsøg med begrænset klinisk værdi.

Artikel 4: Vi gennemgik offentlige dokumenter fra lægemiddelmyndigheder omkring 12 godkendelsesprocedurer for methylphenidat til behandling af voksne med ADHD. I syv af 12 lægemiddelgodkendelser manglede der kliniske forsøg, som vi vidste eksisterede. Den nuværende lovgivning angiver, at al tilgængelig evidens skal inkluderes, når man søger om lægemiddelgodkendelse.

Konklusionen er, at de gavnlige og skadelige effekter af methylphenidat depot-præparater til behandling af ADHD hos voksne og antidepressiv medicin til behandling af voksne med depression er uafklarede på grund af metodemæssige begrænsninger i de kliniske forsøg. Flere af disse metodemæssige begrænsninger anbefales af de europæiske og amerikanske lægemiddelmyndigheder. Slutteligt er methylphenidat som depot-præparat tilsyneladende blevet godkendt på baggrund af udvalgte kliniske forsøg frem for alle tilgængelige kliniske forsøg.

Introduction

Mental health and the use of psychotropic drugs

According to the Global Burden of Disease study, an estimated 970 million people worldwide had a mental health diagnosis in 2017.[1] Depression alone was estimated to affect more than 260 million people and is one of the leading causes of disability.[1] The use of psychiatric drugs has increased over the past 30 years,[2, 3] and for some indications the rise has been steep, such as central stimulants prescribed for use in adults with attention deficit hyperactivity disorder (ADHD).[4-7] In Denmark, ADHD medication use for adults aged 18 years and older rose from 0.3 million defined daily doses prescribed in 2004 to 18.4 million defined daily doses prescribed in 2019.[8] Similarly in Denmark, 10% of those 25 years and older were taking an antidepressant in 2016,[9] whereas in the United States, 13% of those 12 years and older were in 2014 taking an antidepressant.[10]

Benefits and harms of psychiatric drugs

The benefits and harms of commonly used pharmacological treatments for psychiatric diagnoses have been questioned in systematic reviews of randomised clinical trials over the past ten years, including antidepressants for depression in adults[11, 12] and medications for use in children and adolescents with ADHD [13, 14] and for adults with ADHD.[15, 16] A Cochrane review on immediate-release methylphenidate for ADHD in adults[17] was withdrawn from the Cochrane Library after criticism was submitted by several independent research groups, including our team, pointing out that important methodological limitations were not considered in the review.[18, 19] The clinical benefits of these psychiatric drugs have been put into question due to reported limitations of the clinical trials such as short trial durations, problems with maintaining the blind, strict exclusion criteria regarding comorbidities, and a dearth of patient relevant outcomes.[11-16, 19] In 2019, the World Health Organization (WHO) rejected an application to include methylphenidate for ADHD onto the WHO List of Essential Medicines. They argued that the benefits and harms were uncertain.[20, 21]

Extended-release methylphenidate

The focus of two included papers (*Paper 1* and *Paper 4*) was the central stimulant methylphenidate in its extended-release formulation. Methylphenidate inhibits dopamine and norepinephrine reuptake inhibitors centrally, which leads to increased levels of these neurotransmitters.[22] According to the US Food and Drug Administration's (FDA) latest methylphenidate Prescriber Information, "the mechanism of therapeutic action in ADHD is not known".[22] The British National Institute of Health and Care Excellence (NICE) recommends methylphenidate as the drug of choice in its latest ADHD treatment guideline.[23] Several different extended-release formulations are approved for use in adult ADHD. The active component, methylphenidate, is the same across most formulations, except for one formulation (dex-methylphenidate) that uses the right stereoisomer only, whereas the formulations differ in their coating and release mechanisms, which give them different pharmacokinetic profiles and half-lives.[24] The extended-release formulations are now more used than the immediate-release formulations.[25, 26] Previous systematic reviews and meta-analyses of methylphenidate for ADHD in adults[27-33] have relied primarily on published data and they have focused on symptom rating scales, whereas quality of life and functional capacity outcomes have not been assessed. The benefits and harms of extended-release methylphenidate for use in adults with ADHD are therefore unclear.

Publication bias and selective reporting

Publication bias, i.e. the omission to publish clinical trials,[34, 35] as well as selective reporting of trial results and outcome switching,[36, 37] are major challenges in medical science. Turner and colleagues[38] reported in 2008 that 31% of pivotal clinical trials submitted to the FDA as part of new drug applications were not published in medical journals. The requirement of mandatory trial registration in trial registries such as ClinicalTrials.gov and the European Union Clinical Trial Register has improved the rate of prospectively registered clinical trials,[39] but adherence to mandatory results reporting on trial registry websites is poor.[40, 41] Particularly publicly funded trials are underreported and the reasons for this are diverse.[40, 42] The lack of access to clinical trial data therefore remains a main concern for making reliable and unbiased assessments of healthcare interventions.

Publication bias and selective outcome reporting can (partly) be mitigated by including regulatory data in systematic reviews.[43] In 2010, after pressure from the Nordic

Cochrane Centre and the European Ombudsman, the European Medicines Agency (EMA) changed its policy regarding access to clinical trial data submitted to them as part of new drug applications.[44] In 2019, Health Canada began prospectively releasing clinical study reports for newly approved drugs following a court case initiated by BMJ assistant editor Peter Doshi.[45, 46] The first systematic review based entirely on regulatory data, a systematic review on neuraminidase inhibitors for the treatment of influenza published in 2014,[47] came to a less favourable conclusion compared to the original review,[48] which was based on published data only. Works on antidepressants,[49 - 51] and the human papillomavirus (HPV) vaccines[52, 53] have also shown added value of using clinical study reports compared to published literature. Regulatory data are particularly useful for assessing patient relevant outcomes, such as quality of life and harms, which are often underreported in published reports.[54]

The drug regulatory agencies' role in designing pivotal drug trials

The problems of relying on surrogate outcomes in clinical trials, i.e. biomarkers, rating scales, or other outcomes without direct relevance for the patients, has been highlighted and discussed for many years.[55-57] It has been reported that new oncology drugs are mostly approved on the basis of surrogate markers,[58, 59] and that FDA's research guidelines recommend the use of surrogate outcomes in anti-infective pivotal trials.[60] FDA seemingly rely on surrogate outcomes for new drug approvals across many specialities and indications according to their own list of previously used surrogate endpoints in pivotal trials.[61] Both EMA[62] and FDA[63] publish guidelines on how applicants should design and conduct pivotal drug trials for marketing authorisation. EMA publishes such guidelines particularly to ensure a harmonised and standardised procedure for drug approvals across the European National Competent Authorities.[62] Whether such guidelines recommend problematic trial designs, including surrogate outcomes, for pivotal psychiatric drug trials remain to be investigated.

The evidence base for regulatory drug approvals

Before a pharmaceutical company conducts pivotal trials for the purpose of applying for marketing authorisation of a new drug, or for a new indication, the company and the relevant drug regulatory agency will often agree on a 'drug development program'.[64] Such a program will often establish how many clinical trials that should be conducted. However,

whether companies might conduct other trials than those agreed to in the development program is unclear. In Turner and colleagues' antidepressant study,[37] the authors assumed that FDA had access to a complete cohort of conducted antidepressant trials, but it was not explored whether other trials than those submitted to the FDA existed. In the systematic review of neuraminidase inhibitors for influenza based on regulatory documents,[47] it was observed that EMA and FDA had seemingly not assessed all clinical trials prior to approval, but the extent of missed trials across the regulators was not reported.[47] It seems to be a cornerstone for reliable and unbiased drug approvals that the drug regulatory agencies assess all available evidence, primarily to mitigate that pharmaceutical companies may selectively include the most favourable trials in new drug applications. Whether or not drug regulators have access to all trials prior to decision-making have seemingly never been systematically assessed.

Objectives

The research objectives for the four papers were:

1. To assess the benefits and harms of extended-release methylphenidate for ADHD in adults (*Paper 1*).
2. To assess the methodological limitations of the evidence of antidepressants for depression in adults (*Paper 2*).
3. To assess the European Medicines Agency and the US Food and Drug Administration's guidelines on how to design pivotal psychiatric drug trials (*Paper 3*).
4. To assess if drug regulatory agencies were making decisions on select samples of clinical trials in new drug applications for methylphenidate for use in adult ADHD (*Paper 4*).

Description of the research projects

Paper 1. Systematic review of extended-release methylphenidate for ADHD in adults

This was a systematic Cochrane review and the protocol was published in the Cochrane Library in 2017.[65] We included parallel-group, placebo-controlled and active-controlled randomised trials of extended-release methylphenidate for use in adults diagnosed with ADHD. We systematically searched databases of published literature and clinical trial registries, and hand searched drug regulatory agency databases for Drug Approval Packages, Public Assessment Reports and other publicly available regulatory documents. We assessed the risk of bias for all included trials using Cochrane's risk of bias tool.[66] We furthermore focused on three trial characteristics that may impair the external validity: (1) restrictive inclusion criteria regarding psychiatric comorbidity; (2) the use of "enriched design", i.e. the inclusion of participants who have previously been exposed to the drug; and (3) the possibility of introducing withdrawal effects. We meta-analysed our prespecified primary outcomes (functional outcomes, self-reported ADHD symptom improvements, and serious adverse events) and secondary outcomes (quality of life, investigator rated and peer-rated ADHD symptom improvements, severe psychiatric adverse events, cardiovascular variables, and adverse events,) as standardised mean differences (SMD), mean differences (MD), or risk ratios (RR) using random effects meta-analyses with inverse variance weighting.

Paper 2. A reanalysis of a systematic review of antidepressants

We reanalysed a systematic review and network meta-analysis of antidepressants for depression in adults, which was published in 2018 and included 522 randomised clinical trials.[67] Using the systematic review's original data, we reassessed the included trials' risk of bias using Cochrane's risk of bias tool[66] and quality of the evidence using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool.[68] We estimated the effects of several trial characteristics such as trial duration, the use of a "placebo lead-in", which is often called a "wash-out period", and publication bias. For 19 of the 522 included trials, we compared data from the outcomes "total dropout rates" and "dropouts due to adverse events" with the original clinical study reports previously obtained

from the EMA and the British regulator, Medicines and Healthcare product Regulatory Agency (MHRA).

Paper 3. EMA and FDA psychiatric drug trial guidelines

We assessed EMA's Clinical Efficacy and Safety Guidelines and FDA's Guidance Documents on how to design pivotal psychiatric drug trials. We submitted Freedom of Information Act requests to EMA and FDA to access the guideline committee member lists and their declared conflicts of interest. We assessed publicly available stakeholder comments and characterised the stakeholders according to their conflicts of interest related to the pharmaceutical industry and counted the number of stakeholders and number of submitted comments on each guideline. We assessed how the guidelines were produced including how and when the documents were open to public comments. Finally, we assessed the guidelines' trial design recommendations with regard to four trial design characteristics: trial duration; exclusion criteria related to psychiatric comorbidity of the included participants; the use of "enriched design" based on previous response to the treatment; and efficacy outcomes. We put the recommendations in a clinical context to assess the impact on the external validity.

Paper 4: Missing clinical trials in methylphenidate drug applications

We assessed whether drug regulatory agencies made decisions on select samples of clinical trials for a cohort of extended-release methylphenidate drug applications. Based on the Cochrane review's systematic search strategy (*Paper 1*), we created an index of registered and published extended-release methylphenidate trials. In our Cochrane review, we also hand searched databases of publicly available documents from several drug regulatory agencies; the FDA, the Australian Therapeutic Goods Administration (TGA), Canada Health and three European agencies, the Dutch Medicines Evaluation Board (MEB), the German Bundesinstitut für Arzneimittel and Medizinprodukte (BfArM), and the MHRA. We assessed which clinical trials appeared in these publicly available documents and compared them with our index of registered and published trials. We classified any ongoing or completed trial as missing if the trial was either sponsored by the pharmaceutical company that was

applying for the marketing authorisation, or if the trial was publicly funded but the company was otherwise involved in the trial, for instance by helping designing the trial or collecting the data.

We assessed the number of missing clinical trials, the proportion of missing trial participants, and we described each drug application to highlight important findings from the drug approval processes, such as internal disagreements within the agencies about the regulatory decisions. Finally, we assessed the drug regulatory agencies submission requirements and whether applicants are asked to submit all available clinical trials in new drug applications. We searched the drug regulators' websites and relevant legislations, and we sent letters to the regulators with clarifying questions about the individual drug applications and the general approval procedures.

Summary of results and discussion

Paper 1. Systematic review of extended-release methylphenidate for ADHD in adults

General findings

We identified 25 randomised placebo-controlled trials (4,876 participants) and 21 of them reported outcome data. Twelve trials were industry-sponsored, three were publicly funded with industry-involvement, five were publicly funded and one had unclear funding. The trials included six different extended-release methylphenidate formulations. The mean trial duration was eight weeks, the median sample size was 216 participants and the trials started between 1998 and 2019.

We included 172 records of published articles, trial registry entries, regulatory documents, and author correspondence documents, of which 55 records were identified through our hand search of drug regulatory agency databases, pharmaceutical company databases, and author correspondences. We included drug regulatory documents from six drug regulatory agencies for eight of the trials. Using the Cochrane Risk of Bias tool, we assessed all trials to be at high risk of bias, particularly due to selective outcome reporting, attrition bias and risk of unblinding. We assessed all included trials to be at high risk in at least one of the three domains related to external validity, i.e. restricted populations in terms of allowed psychiatric comorbidity, the use of "enriched design", and risk of withdrawal effects. Nine of the 12 industry-sponsored trials were rated as high risk for all three domains.

Short-term follow-up (up to 26 weeks)

Primary outcomes: One trial reported on any functional outcome, 'absence from work/ school/ training'. The mean difference was 0.15 days less absence (95% CI: -1.8 to 2.1 days) at 13 weeks of follow-up for those on methylphenidate compared to placebo. For self-rated ADHD symptoms (15 trials, 3,424 participants), the SMD was 0.38 (95% CI: 0.31 to 0.45) favouring methylphenidate and the risk of serious adverse events (14 trials, 4,078 participants) was RR = 1.43 (CI 95% CI: 0.85 to 2.43).

For our secondary outcomes, quality of life (five trials, 1,513 participants), SMD = 0.12 (95% 0.01 to 0.22) favouring methylphenidate. Investigator-rated ADHD symptoms (19 trials, 4,193 participants), SMD = 0.43 (95% CI: 0.35 to 0.51) favouring methylphenidate and for peer-rated ADHD symptoms, i.e. family or partner rated symptoms, (two trials, 630 participants), SMD = 0.39 (95% CI: 0.22 to 0.57). We did not meta-analyse the "severe psychiatric adverse events" outcome due to sparse data. For the cardiovascular variables, we only found a difference for pulse, which increased 4.2 beats per minute (95% CI: 2.3 to 6.2) on methylphenidate.

The overall dropout rate was similar between methylphenidate and placebo, RR = 1.01 (95% CI: 0.84 to 1.21), whereas dropouts due to adverse events, RR = 2.36 (95% CI: 1.62 to 3.43), the proportion of participants experiencing any adverse event, RR = 1.27 (95% CI: 1.19 to 1.37), and the proportion of participants experiencing psychiatric adverse events, RR = 1.99 (95% CI: 1.54 to 2.58), were higher for those on methylphenidate. We further estimated the risks for experiencing 12 adverse events of interests. All but two events occurred more frequently with methylphenidate, with the risk ratio point estimates ranging from 1.35 (95% CI: 1.18 to 1.54) for headache to 5.52 (95% CI: 2.77 to 10.99) for feeling jittery.

Medium-term and long-term follow-up (up to 52 weeks, 52 weeks or more)

One trial reported on self-reported ADHD symptoms, investigator-rated ADHD symptoms and quality of life at 52 weeks of follow-up. The effect estimates were similar to the short-term results. We included the reported harms' data in the short-term analyses. None of the included trials had a continuous placebo-controlled phase of more than 52 weeks.

Strengths and limitations

To our knowledge, this is the first systematic review of methylphenidate for adult ADHD to include drug regulatory data, such as FDA Drug Approval Packages and Public Assessment Reports. Previous systematic reviews[27-33] have primarily relied on published reports. It may also be the first systematic review to assess functional outcomes, individual adverse effects, peer-rated ADHD symptoms, and to report a summary effect estimate for quality of life. A systematic review previously assessed quality of life in adult ADHD,[69] but the review only included one methylphenidate trial reporting a quality of life outcome.[70] Our results for

self– and investigator rated ADHD symptom improvement and for cardiovascular variables are similar to those in previous reviews.[33, 71, 72]

Despite our efforts to identify regulatory data, the main limitation of our review was the lack of access to clinical study reports and raw trial data. We tried to access clinical study reports from pivotal trials from the German drug regulator, Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), but our request was declined. There has been an ongoing lawsuit between Merck and PTC Therapeutics versus the European Medicines Agency about limiting the access to clinical trial data submitted to drug regulators as part of new drug applications.[73] The European Court rejected the lawsuit in January 2020[74, 75] and thereby confirmed current European transparency policies (policy 0043 and policy 0070)[44, 76] that ensure access to clinical data. Updates of our review should be based entirely on regulatory documents, such as clinical study reports.

We judged all included trials to be at high risk of bias and our results should be interpreted in the light of this uncertainty. The reporting of harms and quality of life outcomes was particularly poor. Due to these limitations and the methodological issues with the included trials, such as low generalisability, short trial durations and high dropout rates, the benefits and harms of extended-release methylphenidate for adult ADHD remain uncertain. We would likely need new, long-term trials that include treatment-naïve participants with psychiatric comorbidities and that use patient-relevant outcomes, to obtain less biased assessments of the benefits and harms of these drugs for use in adult ADHD.

Paper 2: A reanalysis of a systematic review of antidepressants

General findings

We included 522 clinical trials as reported in the original systematic review,[67] of which 304 were placebo-controlled trials. We included clinical study reports from 19 of the included trials. The median trial duration was eight weeks and the longest continuous placebo-controlled trial lasted 36 weeks.

We reassessed the risk of bias of the included trials. When we used the original systematic review's individual risk of bias assessments, we found that one trial had low risk of bias, 383 (73%) had unclear risk and 138 (26%) had high risk. Using our own bias

assessments and assuming all blinding domains had unclear risk of bias, and taking into consideration selective reporting of the review's primary and secondary outcomes, no trial had low risk of bias, 261 (50%) had unclear risk, and 261 (50%) had high risk.

Trials categorised as having a 'placebo lead-in' phase (142 trials) reported an SMD of 0.31 (95% CI: 0.28 to 0.34) on investigator-rated ADHD symptoms, compared to trials without a 'placebo lead-in' (30 trials), which reported an SMD of 0.22 (95% CI: 0.16 to 0.29). There was an effect of publication status on the reported investigator-rated ADHD symptoms, where published trials (196 trials) reported an SMD of 0.33 (95% CI: 0.30 to 0.35) and unpublished trials (57 trials) reported an SMD of 0.15 (95% CI: 0.11 to 0.19). The effect of antidepressants versus placebo was reported in 109 trials as a mean difference on the investigator-rated Hamilton 17-item scale (range 0-52 points). The mean difference was 1.97 points (95% CI: 1.74 to 2.21). For the outcomes of overall dropout rates and dropout due to adverse events, there were discrepancies for 12 of 19 trials (69%) between the clinical study reports and the systematic review. We judged the evidence to be of 'very low' certainty due to high risk of bias, indirectness of the evidence, and publication bias.

Strengths and limitations

The main limitation of our reanalysis was the reliance on data reported in the systematic review,[67] which was mainly derived from published reports. We would need access to clinical study reports, and preferably individual patient data, to address the most important clinically relevant questions regarding the benefits and harms of antidepressants. Our reported 2-point difference between antidepressants and placebo on the most commonly used investigator-rated symptom scale, Hamtilton-17, is similar to the effect estimate in a previous systematic review on selective serotonin reuptake inhibitors.[12] To our knowledge, the impact of using a "placebo-lead in" phase has not previously been estimated. However, it should be noted that it was not clearly described in the original review how the 'placebo lead-in' phase was defined. Our finding that unpublished trials only report effect sizes half of those from published trials is similar to the finding from Turner and colleagues in 2008,[37] but notably, our sample was 3.5 times larger (253 versus 73 trials).

The methodological limitations of antidepressants trials are similar to those identified in our systematic review of extended-release methylphenidate (Paper 1). These were short trial duration, questionable blinding, use of an 'enriched design' and risk of withdrawal effects (captured in our 'placebo lead-in analysis'), as well as a dearth of patient-relevant outcomes.

As of now, it is uncertain whether antidepressants provide more benefit than harm for treating depression in adults compared to placebo. Our conclusion is similar to what we found for extended-release methylphenidate for ADHD in adults; we would need long-term trials that include treatment-naïve participants to assess the beneficial and harmful effects of antidepressants for use in adults.

Paper 3. EMA and FDA psychiatric drug trial guidelines

General findings

We included 13 EMA Clinical Efficacy and Safety guidelines and five FDA Guidance documents. The guidelines covered 15 different psychiatric indications as three had overlapping scopes. Five months from submission of our Freedom of Information Act request regarding access to EMA's guideline committee member lists and their declared conflicts of interest, EMA had not processed it. FDA informed us at a telephone meeting that FDA staff members author Guidance Documents and FDA employees are not allowed to possess financial conflicts of interest. According to FDA policy, there are exceptions to this rule and some employees may have financial interests up to 15,000 US Dollars.[77]

There were available stakeholder comments for six EMA guidelines and four FDA Guidance Documents. Overall, 70 stakeholders submitted comments on the guidelines, which we categorised according to their conflicts of interest; 38 (54%) industry; 18 (26%) not-industry but with industry-related conflicts; 6 (9%) independent; 8 (11%) unclear conflicts. The stakeholders submitted 983 comments; 621 (68%) from industry; 241 (26%) not-industry but with industry related conflicts; 36 (4%) independent; 19 (2%) unclear conflicts); 66 of the comments were not linked to a stakeholder.

EMA and FDA developed the guidelines in similar fashions. Guideline drafts and final versions are made publicly available for comments. Everybody may comment on the documents and both agencies describe that they actively recruit relevant stakeholders. It

was unclear how and to what degree the recruitment of external stakeholders was implemented in practice.

The EMA guidelines contained trial design recommendations for all four characteristics (i.e. trial duration, exclusion criteria related to psychiatric comorbidity, the use of "enriched design", and efficacy outcomes) in 11 of 13 guidelines, and two guidelines contained recommendations for three characteristics. None of the FDA Guidance Documents contained recommendations on all four characteristics. In general, the trial design recommendations were of limited clinical relevance. The recommended trial durations were short (often weeks) compared to the expected course of the conditions (often chronic); EMA's guidelines were restrictive regarding allowed psychiatric comorbidity whereas FDA's guidelines emphasised that unnecessary restrictions should be avoided; most EMA guidelines stated that participants could have been exposed to the drug before enrolment; and most guidelines recommended the use of rating scales or other surrogate outcomes rather than objective or functional outcomes.

Strengths and limitations

To our knowledge, this is the first systematic assessment of the development and stakeholder involvement of EMA and FDA's regulatory guidelines on drug trial design recommendations. Recently, a study was published regarding FDA's infectious disease Guidance Documents.[61] Similar to our findings, it was reported that FDA mostly recommended surrogate outcomes, such as viral load, rather than hard outcomes, such as mortality. In our analysis, we assessed three further trial characteristics, i.e. trial duration, exclusion criteria, and the use of an "enriched design". It would be Informative to assess these trial design recommendations for other specialties, such as oncology, where the patient-relevance of using surrogate outcomes, such as progression free survival, has been questioned.[78, 79]

The main limitation of the study was the small sample of guidelines and available stakeholder comments. It may therefore be difficult to generalise across specialities and indications. In some cases, it was not easy to categorise the stakeholders according to their conflicts of interest and it may also be debated what constitute clinically relevant trial designs. We tried to base our assessment of the recommended trial designs' clinical

relevance according to the guidelines themselves to avoid making subjective judgements. Additionally, the EMA has not yet responded to our Freedom of Information Act request due to reduced work capacity after their relocation to Amsterdam. It will be important to assess the EMA guideline committee members' conflicts of interest, once we receive them. Regardless of these limitations, our results indicate a dearth of non-industry stakeholder involvement in the guideline development. The trial recommendations may contribute to research waste by recommending trial designs that do not address clinically relevant questions.

Our research highlights several areas that can be improved. It seems sensible that the drug regulatory agencies prospectively disclose the committee members of such guidelines and their declared conflicts of interest. More importantly, it seems needed with more proactive recruitment of non-conflicted stakeholders to help refine trial design recommendations to include patients' and the public's priorities in psychiatric research.

Paper 4: Missing clinical trials in methylphenidate drug applications

General findings

We included 18 extended-release methylphenidate trials, of which 16 were industry-sponsored and two were publicly funded trials with industry-involvement. We identified publicly available regulatory documents related to 12 drug applications of six different methylphenidate formulations. The documents were published by six different drug regulatory agencies; the FDA (three applications), Canada Health (three), the TGA (two), MHRA (two), BfArM and MEB (one each). Ten applications were approved for market authorisation and two were rejected.

We found missing clinical trials in seven of the twelve regulatory documents related to new drug applications. The number of missing trials ranged from one to six and the proportion of missing trial participants in the seven drug applications ranged from 14% to 72%.

All the agencies we contacted responded to our Freedom of Information Act requests. The FDA and Australia's Therapeutic Goods Administration partially addressed our questions but asked us to request specific documents, such as specific parts of the clinical

study reports. BfArM and Health Canada fully addressed our question about the missing trials. Health Canada sent us the Clinical Study Report Module 2.7, which contains a list of all clinical trials submitted with the drug application.[80] FDA, TGA, Health Canada and EMA's submission requirements seem to specify that the applicants must submit all available clinical trials "*pertinent*" to the drug applications. However, it is not clear how "*pertinent*" should be interpreted from current guidelines and legislations.

Strengths and limitations

To our knowledge, this is the first systematic assessment of the completeness of new drug applications with regard to the inclusion of all available clinical trials at the time of approval. In the neuraminidase inhibitor review for influenza it was observed that FDA and EMA "largely ignored" the largest clinical trial M76001 (p. 28),[47] but the extent of missing trials was not systematically reported across the different oseltamivir drug applications.

Our study has many limitations. Foremost, we relied on publicly available documents, apart from Health Canada's approval of OROS methylphenidate, and the agencies may have had access to more trials and more data than appeared in the documents. We did not approach all regulators regarding all applications due to the long response time and the absence of clear answers to our initial requests. It therefore seemed unfeasible that we could confirm all our results with the regulators. However, at least in three cases it seems certain that the agencies did not assess all trials before decision-making: FDA and Health Canada's approval of OROS methylphenidate and BfArM's approval of extended-release methylphenidate, respectively.

Our sample of drug regulatory documents was small and our findings may not be generalisable across drug regulatory agencies, drugs, conditions, or over time. It is also uncommon to share regulatory documents on rejected drug applications and we may therefore have missed additional rejections. To fully assess the implications of our findings, it would be useful with large-scale assessments of drug approvals for cohorts of different drugs and indications.

We have demonstrated that it is possible for drugs to get approved on a seemingly select sample of trials. Whether the applicants did not submit all available trials or the drug regulatory agencies did not disclose all trials they based their decisions on, or both, is

unclear. Regardless, there may be a potentially serious deficiency in the current regulatory system.

Several steps in the current drug approval procedure could be strengthened. First, it seems needed with a clarification of the submission requirements. It is unclear what "*pertinent trials*" entails, and it may provide leeway for applicants to not submit all trials and for drug regulators to not assess all available trials. Second, drug regulatory agencies should conduct their own systematic searches, primarily of trial registries, to ensure they do not miss important clinical trials. Finally, it would increase transparency if drug regulators prospectively disclosed the evidence basis for new drug approvals, with cross-links to trial registry entries of the included clinical trials to clearly communicate which trials were included in the new drug applications.

Conclusion and perspective for further research

Overall conclusion

Overall, we have found that clinical trials of extended-release methylphenidate for adult ADHD and antidepressants for depression in adults were affected by several methodological limitations and that the benefits and harms of these drugs therefore remain uncertain. We found that the drug regulators play a crucial role in the design of pivotal psychiatric drug trials and that they recommend trial designs of questionable clinical relevance. We also found that seven of 12 drug approvals of extended-release methylphenidate may have been affected by the absence of entire clinical trials.

To improve the quality and clinical relevance of pivotal psychiatric drug trials that form the basis for new drug applications, and also appear in systematic reviews and inform clinical guidelines, we need to address the problem at its origin. These methodological limitations may partly be explained by the drug regulators' own recommendations. Currently, the majority of those involved in shaping these recommendations are predominantly pharmaceutical companies or other stakeholders with conflicts of interest, which may affect the research priorities.

The potential breach we identified in the drug approval procedures of extended-release methylphenidate for adult ADHD emphasise the importance of transparent drug

approval procedures. It should be clearly communicated on what basis regulatory agencies make decisions, and new drugs should be approved based on all available evidence, not just subsets of the most favourable trials.

Implications for future practice

Based on this thesis, we have identified three areas that ought to be improved for the benefit of psychiatry and evidence-based clinical practice:

(1) Long-term clinical trials of methylphenidate for adults with ADHD and antidepressants for depression in adults seem needed. These trials should be conducted with treatment-naïve participants and they should address whether these drugs are beneficial on patient-relevant outcome measures.

(2) Drug regulatory agencies should actively include patients and non-conflicted researchers and organisations in their guideline development of trial design recommendations for pivotal psychiatric drug trials.

(3) Drug regulatory agencies should transparently disclose which trials underlie new drug approvals and ensure they do not make decisions on select samples of clinical trials by having unambiguous submission requirements.

Abbreviations

ADHD	Attention deficit hyperactivity disorder
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
CI	Confidence interval
DSM	Diagnostic and Statistical Manual of Mental Disorders
EMA	European Medicines Agency
FDA	US Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICD	International Classification of Diseases
MEB	Medicines Evaluation Board
MHRA	Medicines and Healthcare products Regulatory Agency
MD	Mean difference
NICE	National Institute for Health and Care Excellence
OROS	Osmotic-controlled release oral delivery system
SMD	Standardised mean difference
TGA	Australian Therapeutic Goods Administration
WHO	World Health Organization

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Paper 1

Extended-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults: Systematic review with meta-analyses of published and unpublished data.

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Submitted for publication

GRADUATE SCHOOL OF HEALTH AND MEDICAL SCIENCES
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Extended-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults: Systematic review with meta-analyses of published and unpublished data.
Cochrane Database of Systematic Reviews 2020, Issue 7. Art. No.: CD012857.
DOI: 10.1002/14651858.CD012857.pub2.

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[Intervention Review]

Extended-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults: Systematic review with meta-analyses of published and unpublished data

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Editorial group: Cochrane Developmental, Psychosocial and Learning Problems Group.
Publication status and date: New, published in Issue 7, 2020.

Citation: Boesen K, Paludan-Müller AS, Gøtzsche PC, Jørgensen KJ. Extended-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults: Systematic review with meta-analyses of published and unpublished data. *Cochrane Database of Systematic Reviews* 2020, Issue 7. Art. No.: CD012857. DOI: 10.1002/14651858.CD012857.pub2.

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ABSTRACT

Background

Attention deficit hyperactivity disorder (ADHD) is a psychiatric diagnosis increasingly used for adults. The recommended first-line treatment is central stimulants, such as methylphenidate, but the benefits and harms remain uncertain.

Objectives

To assess the benefits and harms of extended-release formulations of methylphenidate for ADHD in adults.

Search methods

We searched databases of published literature and clinical trial registries (Nov 2017 and March 2019), cross-referenced published reports, contacted trial authors, and searched pharmaceutical company databases and 12 drug regulatory agency databases for clinical trial data.

Selection criteria

Randomised, parallel-group trials comparing extended-release methylphenidate formulations with placebo or other ADHD medications in adults diagnosed with ADHD.

Data collection and analysis

Two review authors extracted data. We assessed dichotomous outcomes as risk ratios (RR), and rating scales and continuous outcomes as mean differences (MD) or standardised mean differences (SMD). We used Cochrane's risk of bias tool and GRADE to assess the certainty of the evidence and meta-analysed using the random effects model. We assessed three trial design characteristics that may impair the generalisability (exclusion of participants with psychiatric comorbidity, responder selection, and risk of withdrawal effects). Our prespecified outcomes were functional outcomes, self rated ADHD symptoms, serious adverse events, quality of life, ADHD symptoms rated by family members and by investigators, severe psychiatric adverse events, cardiovascular variables, and adverse events.

Main results

We included 25 trials (4,876 participants) and 21 trials provided outcome data. We included documents from six drug regulatory agencies covering eight trials. Thirteen trials (79% of participants) were industry sponsored, four (15%) were publicly funded with industry-involvement, eight (6%) were public, and one had unclear funding. The median trial duration was eight weeks. All trials were rated at high risk of bias, primarily due to unclear blinding of participants and investigators, attrition bias, and selective outcome reporting. All trials were impaired in at least one of the three domains regarding generalisability and 12 industry-sponsored trials were impaired in all three

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domains. For the primary outcomes, methylphenidate had no significant effect on 'days missed at work' (MD 0.15 days, 95% CI: -1.81 to 2.11), or serious adverse events (RR 1.43, CI 95% CI: 0.85 to 2.43), whereas methylphenidate improved self-rated ADHD symptoms (SMD 0.38, 95% CI: 0.31 to 0.45). For secondary outcomes, methylphenidate had an effect on self-rated quality of life (SMD 0.12, 95% CI: 0.01 to 0.22), investigator rated ADHD symptoms (SMD 0.43, 95% CI: 0.35 to 0.51) and ADHD symptoms rated by family members (SMD 0.39, 95% CI: 0.22 to 0.57). For cardiovascular variables, methylphenidate increased the pulse (4.3 beats per minute, 95% CI: 2.3 to 6.2) but not blood pressure. We did not meta-analyse "severe psychiatric adverse events" due to sparse data. The risk of overall dropout was similar between methylphenidate and placebo (RR 1.01, 95% CI: 0.84 to 1.21), whereas methylphenidate increased the risk of dropout due to adverse events (RR 2.36, 95% CI: 1.62 to 3.43), any adverse event (RR 1.27, 95% CI: 1.19 to 1.37) and any psychiatric adverse event (RR 1.99, 95% CI: 1.54 to 2.58). We assessed 12 specific adverse events, of which all but two occurred more frequently for methylphenidate. We rated the certainty of the evidence as 'very low' for all outcomes primarily due to high risk of bias and indirectness.

Authors' conclusions

Extended-release methylphenidate did not reduce 'days missed at work' and the effect on quality of life was negligible. It improved ADHD symptoms measured on rating scales, but caused harms. Our certainty in the evidence is 'very low' due to high risk of bias, short trial durations, and low generalisability. The benefits and harms of extended-release methylphenidate remain uncertain.

PLAIN LANGUAGE SUMMARY

[Extended-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults]

Review question

This review addressed the beneficial and harmful effects of methylphenidate given as slow-release pills, compared to placebo. We particularly focused on functional capacity, such as days absent from work, and patient-centred outcomes such as patient-rated symptoms and quality of life.

Background

Attention deficit hyperactivity disorder (ADHD) is a psychiatric diagnosis that increasingly more adults get and receive drugs for. The recommended first-line drug is methylphenidate, a central stimulant related to amphetamine. There is uncertainty about the drug's effectiveness, especially for patient-centred outcomes and the drug's harms.

Study characteristics

We found 25 studies with 4,876 participants that compared extended-release methylphenidate with placebo. Half of the studies were sponsored by the companies that sell the drugs. The studies lasted a median of 8 weeks.

Key results

Methylphenidate had some effect on ADHD symptoms rated by the participants, family members or spouses, and investigators. The drug did not reduce days missed at work or improve quality of life rated by the participants. There was no increased risk of serious harms, but the drug caused many non-serious harms. It increased the risk of experiencing any type of adverse event and psychiatric adverse events, increased the heart rate and the risk of dropping out of the studies due to adverse events.

Quality of the evidence

The certainty of the evidence that benefits are greater than the harms is very low. All studies were at high risk of bias, which means that the reported results were not reliable. We identified many problems with the design of the studies, e.g. participants with other psychiatric diagnoses than ADHD were often excluded from the studies although ADHD patients in a clinical setting often also have other psychiatric diagnoses, and often only participants who had previously tolerated methylphenidate or similar drugs were allowed to participate.

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SUMMARY OF FINDINGS

Summary of findings 1. Extended-release methylphenidate compared to placebo for ADHD

Extended-release methylphenidate compared to placebo for ADHD

Patient or population: ADHD
Setting:
Intervention: extended-release methylphenidate
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with extended-release methylphenidate				
[Functional outcome] Days missed at work/ school/ training		MD 0.15 days fewer (2.11 fewer to 1.81 more)	-	409 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [1,2]	
ADHD symptoms (self rated)	The mean ADHD symptoms (self rated) was 0	SMD 0.38 lower (0.45 lower to 0.31 lower)	-	3424 (16 RCTs)	⊕⊖⊖⊖ VERY LOW [1,2]	
Serious adverse events	Study population		RR 1.43 (0.85 to 2.43)	4078 (14 RCTs)	⊕⊖⊖⊖ VERY LOW [1,2]	
	12 per 1,000	17 per 1,000 (10 to 30)				
Quality of life (self rated)	The mean quality of life (self rated) was 0	SMD 0.11 lower (0.22 lower to 0.01 lower)	-	1513 (6 RCTs)	⊕⊖⊖⊖ VERY LOW [1,2]	
ADHD symptoms (investigator rated)	The mean ADHD symptoms (investigator rated) was 0	SMD 0.43 lower (0.51 lower to 0.35 lower)	-	4213 (20 RCTs)	⊕⊖⊖⊖ VERY LOW [1,2]	
ADHD symptoms (peer rated)	The mean ADHD symptoms (peer rated) was 0	SMD 0.39 lower (0.57 lower to 0.22 lower)	-	630 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [1,2]	
Adverse events (proportion experiencing any adverse event)	Study population		RR 1.27 (1.19 to 1.37)	4214 (14 RCTs)	⊕⊖⊖⊖ VERY LOW [1,2]	
	641 per 1,000	814 per 1,000 (763 to 878)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

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CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] All trials were rated at high risk of bias
[2] All trials had limited generalisability

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BACKGROUND

Description of the condition

The diagnostic criteria for adult attention deficit hyperactivity disorder (ADHD) differ between the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) and the International Classification of Disorders (ICD-11) and have changed over time (Lange 2010). The DSM-V criteria require the presence of five or more symptoms of inattention or hyperactivity/ impulsivity that affect social, academic and/or work/ school functioning, which should have been present before the age of 12 years (APA 2013). The ICD-11 criteria are similar but do not define an age cut-off for symptom occurrence (WHO 2019a).

A systematic review of epidemiological studies (Simon 2009) reported a pooled prevalence of adult ADHD of 2.5%, and the most recent World Health Organization (WHO) Mental Health Survey reported a prevalence of 2.8% across ten countries (Fayyad 2017). Adults with ADHD often have psychiatric comorbidities (Kessler 2006, Jacob 2007, Sobanski 2007a, Cumyn 2009, Groß-Lesch 2013, Philipsen 2014) such as depression, anxiety or substance abuse disorders. The youngest children in a school class have a higher risk of getting an ADHD diagnosis than the oldest (Elder 2010, Evans 2010, Morrow 2012, Sayal 2017, Layton 2018, Root 2019), and follow-up epidemiological studies have reported between 5 to 22% of those diagnosed in childhood fulfil the diagnostic ADHD criteria in adulthood (Faraone 2006, Moffitt 2015, Caye 2016, Agnew-Blais 2016). For these reasons, the adult ADHD diagnosis and its categorisation as a “neurodevelopmental disorder", the treatment modalities, the impact of socioeconomic factors, and the natural course for those diagnosed are debated (Barkley 2002, Timimi 2004, Bailly 2005, Weiss 2007, Asherson 2010, Moncrieff 2010, MHRA 2010, MEB 2016).

Description of the intervention

Methylphenidate is a central stimulant related to amphetamine. It inhibits dopamine and noradrenergic reuptake transporters, thus increasing the synaptic concentration of these neurotransmitters (Challman 2000, Iversen 2006). Methylphenidate can be administered as immediate-release or extended-release oral tablet formulations. The extended-release formulations use different coatings and release mechanisms to ensure a prolonged release of methylphenidate (Coghill 2013, Maldonado 2013), and they are prescribed more frequently than immediate-release formulations (Treceño 2012, Beau-Lejdstrom 2016).

The UK National Institute for Health and Care Excellence (NICE) recommends methylphenidate as the first-line drug for ADHD in adults (NICE 2018, section 1.7.11). The WHO rejected in 2019 an application to include methylphenidate on the WHO Model list of Essential Medicines submitted by faculty at the Icahn School of Medicine (WHO 2019b, Storebø 2020). The WHO argued there were uncertainties regarding the benefits and harms and low quality of the evidence (WHO 2019c, p. 441). The WHO highlighted that a Cochrane review of immediate-release methylphenidate (Epstein 2014) was retracted in 2016 since the review authors were unable to respond to criticism of the methodological limitations of the included trials (Epstein 2016, Boesen 2017).

How the intervention might work

Methylphenidate has central and peripheral stimulatory effects. The central effects are primarily due to increased synaptic concentration of dopamine and norepinephrine, which are suggested to have behavioural and cognitive effects in adults with ADHD (Foquest 2019, p. 22), but the exact mode of therapeutic action is unknown (FDA 2017, p. 20). A systematic review of single-dose methylphenidate studies in healthy adults reported improvement for several cognitive domains (Linssen 2014). Methylphenidate is used as a cognitive enhancement drug by students and adults (Sussman 2006, Wilens 2008, Franke 2013). Its peripheral stimulatory effects include increases in heart rate and blood pressure (Mick 2013). Observational studies of stimulant use in children and in adults have reported an increased risk of cardiovascular events (Holick 2009, Schelleman 2012, Dalsgaard 2014, Shin 2017) or no increased risk (Cooper 2011, Habel 2011). The FDA Prescriber Information warns about serious cardiovascular events (FDA 2017, section 5.1).

Long-term observational follow-up studies from the Multimodal Treatment of ADHD (MTA) study in children (MTA 1999) have not found beneficial effects on functional outcomes such as hospital admissions, delinquency, or academic performance for those treated with methylphenidate compared to no treatment after three to eight years of follow-up (Jensen 2007, Molina 2007, Molina 2009). Methylphenidate increase metabolic turnover, which may lead to stunted growth. At 16 years of follow-up, those consistently taking methylphenidate were on average 5 cm shorter than those with the lowest methylphenidate intake (Swanson 2017).

Why it is important to do this review

In the United Kingdom, the prescription rate of ADHD drugs for adults between 25 and 45 years of age rose 16-fold from 3.4 per 10.000 in 2000 to 53 per 10.000 in 2015 (Renoux 2016). Across 14 countries, the annual average increase in ADHD medication use was 18% between 2001 and 2015 (Raman 2018).

Previous systematic reviews (Faraone 2004, Peterson 2008, Koesters 2009, Meszaros 2009, Faraone 2010, McDonagh 2011, Castells 2011, Castells 2013, McDonagh 2015, Cunill 2016, Cortese 2018) have assessed methylphenidate compared to placebo. These reviews have mostly relied on published literature and assessed symptom-rating scales, which might not be the most patient-relevant outcomes. A systematic review of patient preference studies (Schatz 2015) included three surveys of adult ADHD patients, which all ranked work and school performance and social contacts most important (Mühlbacher 2009, Mühlbacher 2010, Glenngård 2013).

Due to substantial selective reporting (McDonagh 2011) and a dearth of patient-centred outcomes in previous reviews, the benefits and harms of methylphenidate for adult ADHD therefore remain uncertain.

OBJECTIVES

To assess the beneficial and harmful effects of extended-release formulations of methylphenidate in adults diagnosed with ADHD.

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METHODS

Criteria for considering studies for this review

Types of studies

Double-blind, parallel-group, randomised controlled trials (RCTs).

Types of participants

Adults diagnosed with ADHD, according to the DSM (APA 1987, APA 2000, APA 2013) or ICD (WHO 1992, WHO 2019a) criteria. Adults were diagnosed according to the criteria of ADHD in childhood, before the introduction of the ADHD diagnosis in adolescence and adulthood with the DSM-5 (APA 2013) and ICD-11 (WHO 2019a).

Types of interventions

Methylphenidate in any extended-release formulation, at any dose, compared with placebo or an active control, or both. We permitted cointerventions, such as cognitive behavioural therapy, and also pharmaceutical interventions, provided they were delivered to both groups.

Types of outcome measures

Primary outcomes

1. Functional outcomes (functional capacity), e.g. academic and job adherence measured as days of lost work or study activities (Philipsen 2008).
2. Self-rated ADHD symptoms a measured on validated rating scales such as the Connors' Adult ADHD Rating Scale (Conners 1999).
3. Serious adverse events as defined according to the *International Council for Harmonisation* (ICH) guideline (ICH 2003).

Secondary outcomes

1. Investigator-rated ADHD symptoms, measured on a validated rating scale.
2. Peer-rated ADHD symptoms (spouse, family or friends), measured on a validated rating scale.
3. Adverse events other than serious adverse events.
4. Cardiovascular variables (i.e. blood pressure and heart rate).
5. Severe psychiatric adverse events, i.e. any psychiatric adverse event classified as “severe” or “serious”, any psychiatric event leading to dose reduction, or to dropout.
6. Quality of life measured on validated scales such as the Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form (Mick 2008).

We used data with the longest possible follow-up within three outcome periods: short term (up to six months), medium term (up to 12 months) and long term (more than 12 months).

Search methods for identification of studies

Electronic searches

We searched for eligible studies in the following electronic sources.

1. Cochrane Central Register of Controlled Trials (CENTRAL; current issue), in the Cochrane Library, which includes the Cochrane Developmental, Psychosocial and Learning Problems Specialised Register.
2. MEDLINE Ovid (1946 onwards).
3. MEDLINE In-Process & Other Non-Indexed Citations Ovid (current issue).
4. MEDLINE Epub Ahead of Print Ovid (current issue).
5. Embase Ovid (1980 onwards)
6. PsycINFO Ovid (1806 onwards).
7. *Cochrane Database of Systematic Reviews* (CDSR; current issue), part of the Cochrane Library.
8. Database of Abstracts of Reviews of Effects (DARE; current issue), part of the Cochrane Library.
9. CINAHL Plus EBSCOhost (Cumulative Index to Nursing and Allied Health Literature; 1937 onwards).
10. Conference Proceedings Citation Index - Science Web of Science (CPCI-S; 1990 onwards).
11. LILACS (Latin American and Caribbean Health Science Information database; www.lilacs.bvsalud.org/en).
12. ClinicalTrials.gov (clinicaltrials.gov).
13. EU Clinical Trials Register (clinicaltrialsregister.eu).
14. ISRCTN Registry (www.isrctn.com).
15. WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch; all available years).

We searched Ovid MEDLINE using the strategy in Appendix 1, which we adapted for the other databases, as necessary. We did not limit the search by publication date or language.

Searching other resources

We searched 12 drug regulatory agency databases for available trial data: The US Food and Drug Administration (FDA), the European Medicines Agency (EMA), Health Canada, the Australian Therapeutic Goods Administration (TGA), the German Bundesinstitut fur Arzneimittel und Medizinprodukte (BfArM), the Dutch Medicines Evaluation Board (MEB), the British Medicines and Healthcare products Regulatory Agency (MHRA), the Heads of Medicines Agency database, the Japanese Pharmaceuticals and Medical Device Agency, the French Agence Nationale de Sécurité du Médicament et des Produits de Santé, the Irish Health Product Regulatory Authority and SwissMedic for all publicly available documents (eTable 1). We searched methylphenidate manufacturer databases of clinical trials including the Yale University Open Data Access (YODA), which contains Johnson & Johnson trials, Novartis’ database, and Purdue’s and Medice’s websites. We contacted all corresponding trial authors and cross-checked all records for eligible data, documents and publications. See Appendix 1 for detailed search strategies.

Data collection and analysis

Selection of studies

Two review authors (KB and ASP) independently screened titles and abstracts using Covidence 2015. Full-text reports of potentially eligible studies were compared against the inclusion criteria. Disagreements were resolved by discussion with a third review author (KJ). We listed the reasons for exclusion of full-text reports in the PRISMA diagram (Moher 2009).

Data extraction and management

Two review authors (KB and ASP) independently extracted study data using a prespecified data extraction sheet and compared data.

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Disagreements were resolved by discussion with a third author (KJ). One review author (KB) entered data into Review Manager 5 (Review Manager 2014), and a second review author (ASP) double-checked.

Assessment of risk of bias in included studies

Two review authors (KB and ASP) independently assessed each trial for risk of bias using the original Cochrane 'Risk of bias' tool (Higgins 2011a). Consensus was sought, and disagreements were resolved through discussion with a third author (KJ). The 'Risk of bias' tool consists of seven domains and each domain was attributed a rating of low risk of bias, unclear risk of bias or high risk of bias.

1. Random sequence generation (selection bias): Was the sequence generated adequately (e.g. computer-generated) or inadequately (e.g. using the day of study enrolment) to allocate participants?
2. Allocation sequence concealment (selection bias): Was the implementation of the randomisation sequence adequate (e.g. central allocation by a third party) or inadequate (e.g. open allocation or using non-opaque envelopes)?
3. Blinding of participants and personnel (performance bias): Methylphenidate's effects may compromise blinding of participants and investigators. We rated the trials as unclear risk of bias, unless the blinding was tested and confirmed. We applied the same method to trials that added active components to the placebo pill, e.g. folic acid in the Levin 1998a and Levin 1998b trials, to mimic adverse effects like stomach-ache and decreased appetite.
4. Blinding of outcome assessment (detection bias): We applied the same method for this domain as described above for blinding of participants and personnel.
5. Incomplete outcome data (attrition bias): We based our assessment on four variables: (1) dropout rates in each arm; (2) dropout rates in each arm due to adverse events; (3) the statistical method used to account for missing data. Proper methods would include multiple imputations, whereas improper methods would include completers' analysis and last observation carried forward (Lachin 2016); (4) other aberrations, e.g. in Casas 2008 and Huss 2010, the combination of high dropout rates and last observation carried forward meant that more participants were categorised as "responders", i.e. benefitted from the drug, than the number of participants completing the trials. There is no dropout level that eliminates the risk of bias, unless it is zero, and we did not define a lower threshold to guide our assessment.
6. Selective outcome reporting (reporting bias): We assessed a trial at high risk of bias, if it prespecified one of our primary or secondary outcomes in a trial registry, protocol, or published report, but did not report it. We categorised any adverse event-reporting threshold (i.e. that a certain percentage of participants must experience an adverse event before it is reported) as reporting bias.
7. Other potential sources of bias: Was the study free of other sources of bias such as baseline differences?

Specific limitations to the generalisability (external validity)

We assessed three study design characteristics related to the generalisability of ADHD drug trials. We depicted these three domains as additional items within the Cochrane 'Risk of bias' tool, and rated them at high, low or unclear risk of limiting the external validity of each trial. These domains should not be mistaken for additional 'Risk of bias' domains (internal validity). Rather, they informed our assessment of "indirectness" when we graded the certainty of the evidence (see Data synthesis).

1. Psychiatric comorbidity

Adults with an ADHD diagnosis are often also diagnosed with other psychiatric diagnoses, such as depression, anxiety or substance abuse (Kessler 2006, Jacob 2007, Sobanski 2007a, Cumyn 2009, Groß-Lesch 2013, Philipsen 2014), and the exclusion of participants with psychiatric comorbidity will likely reduce the trials' generalisability (Surman 2010). It has also been suggested that such exclusions could lead to an overestimation of the treatment effect (Pliszka 1989; Sobanski 2007b, MHRA 2010).

1. Low risk: Participants diagnosed with other psychiatric diagnoses than ADHD were not excluded, unless methylphenidate was contraindicated (e.g. bipolar affective disorder or suicidality).
2. Unclear risk: There was no, or an unclear, description whether participants with psychiatric comorbidity were allowed.
3. High risk: Participants with psychiatric comorbidities other than ADHD, or psychiatric symptoms, were excluded from participating in the trial.

2. Responder selection ('enriched design')

Some patients do not benefit from or tolerate methylphenidate and are referred to as "non-responders" (Elia 1991; de Sonneville 1994; Cho 2007). It is ethically unacceptable to include participants who are known to experience harm or to not benefit from the intervention. However, the exclusion of such participants will lead to an overestimation of benefits and an underestimation of harms compared to a treatment-naïve population, especially if only participants known to benefit from the drug are included. Selecting participants based on previous exposure to the drug is called an 'enriched design' (FDA 2019).

1. Low risk: Participants were treatment-naïve.
2. Unclear risk: There was no, or an unclear, description of exclusion criteria or of previous stimulant use.
3. High risk: Previous exposure to methylphenidate, or other stimulants, was allowed, and /or 'non-responders' (or similar) were excluded before randomisation.

3. Withdrawal effects

Stimulant use can lead to dependence and tolerance (FDA 2017). Therefore, if participants take stimulants upon enrolment and stop treatment before randomisation, they might experience withdrawal effects. If the taper (often called a "washout") is not of sufficient duration, withdrawal or rebound symptoms may occur during the trial (Cox 2008, Recalt 2019).

1. Low risk: Participants were treatment-naïve, or the stimulant-free period before randomisation was of such duration that the risk of withdrawal effects was considered minimal.
2. Unclear risk: There was no, or an unclear, description of the participants' treatment status, or it was uncertain if the stimulant-free period prior to randomisation was sufficient to avoid withdrawal effects.

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3. High risk: Stimulants were stopped before randomisation, with a washout phase of insufficient duration or without a washout.

Measures of treatment effect

Dichotomous data

We summarised dichotomous data as risk ratios (RR) with corresponding 95% confidence intervals (95% CIs).

Continuous data

For continuous data and rating scales, we extracted mean change or endpoint data (preferred) and the corresponding standard deviations (SDs) or standard errors (SEs) to calculate a mean difference (MD) or a standardised mean difference (SMD) with 95% CIs.

Unit of analysis issues

Cross-over trials

We excluded cross-over trials due to the risk of carry-over stimulant effects and the likely loss of blinding. In a trial of immediate-release methylphenidate (Gualtieri 1985), all eight participants were able to correctly guess their allocation, probably due to the adverse events.

Studies with multiple time points

We split up outcome periods into short term (up to six months), medium term (up to 12 months), and long term (more than 12 months). If a trial reported multiple sets of study data within the same predefined outcome period, we extracted data with the longest follow-up time.

Studies with multiple treatment groups

In studies with multiple methylphenidate groups and a single comparator arm, we pooled the groups to make a single, pair-wise comparison (Higgins 2011b).

Dealing with missing data

A drug class review from 2011 reported that a considerable amount of data were missing in ADHD drug trials (McDonagh 2011). Besides searching for unpublished and regulatory data, as described elsewhere, we took the following precautions:

1. We highlighted unreported trial outcomes in the 'selective outcome reporting' bias domain.
2. We imputed missing SDs based on trials using the same scale and of similar size.
3. We extracted and meta-analysed the overall dropout rates. We used the full population sizes rather than restricted populations, e.g. per-protocol populations or 'safety-populations'.
4. We highlighted each trial's statistical method for dealing with missing data, e.g. last observation carried forward (LOCF), in the 'attrition bias' domain.
5. We preferred analyses based on imputed rather than completer's data, and made it clear if such a choice was made.

Assessment of heterogeneity

We assessed clinical heterogeneity related to differences in the trial populations, interventions or settings. We assessed methodological heterogeneity using the Cochrane 'Risk of bias' tool and the three domains related to the trials' generalisability (psychiatric comorbidity, responder selection, and withdrawal effects). We assessed statistical heterogeneity using the I^2 statistic and Chi^2 test (Deek 2011) and also considered the results of our prespecified subgroup and sensitivity analyses.

Assessment of reporting biases

We describe in detail elsewhere how we assessed outcome reporting bias (Assessment of risk of bias in included studies). We assessed publication bias and other small study effects, using funnel plots with estimated effect sizes plotted against their standard error (Egger 1997), if 10 or more studies reported a given outcome (Sterne 2011).

Data synthesis

We summarised data using random-effects meta-analyses with inverse-variance weighting due to anticipated clinical, methodological and statistical heterogeneity (McDonagh 2011; Storebø 2015). We considered all studies eligible for meta-analysis regardless of their risk of bias assessment and methylphenidate dosage, as there is no established dose-response relationship (NICE 2009).

Summary of findings

We created a 'Summary of findings' table for the primary outcomes and some of the secondary outcomes with placebo comparisons. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate the certainty ('high', 'moderate', 'low', or 'very low') in the effect estimate for each outcome according to five elements: risk of bias, publication bias, imprecision, inconsistency and indirectness (Schünemann 2013).

Subgroup analysis and investigation of heterogeneity

We prespecified to conduct subgroup and sensitivity analyses when the I^2 was greater than 50%.

1. Psychiatric comorbidity: Trials that excluded participants with psychiatric comorbidity compared to trials that did not.
2. Responder selection: Trials with responder selection ('enriched design') compared to trials without responder selection.
3. Withdrawal effects: Trials with high risk of withdrawal effects compared to trials with a low risk of withdrawal effects.
4. Conflicts of interest: Industry-sponsored trials compared to other trials.

Sensitivity analysis

1. Restricting the analyses to trials with low risk of attriton bias according to our bias assessment.

Post-hoc amendments

Serious adverse events

We based our meta-analysis on the number of participants experiencing one or more serious adverse event. For trials that did not report on the unit of analysis, e.g. number of participants or number of events, we assumed the number of participants and events were the same. E.g. if a trial reported three serious

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adverse events, we assumed three participants had experienced three events in total, i.e. one event per participant.

Mean difference subgroup analyses of symptom rating scales

Mean differences on a rating scale are more clinically relevant than a unitless standardised mean difference. Therefore, we also reported the mean differences based on the rating scales used in the trials. We grouped scales assessing the same items and using the same range.

Harms' analyses

We pooled adverse events and serious adverse events from the short-term and medium-term periods, as only one trial reported medium-term data. We wanted to avoid splitting up the analyses and since we used risk ratios, we considered it a feasible method.

Subgroup and sensitivity analyses

We did not conduct two prespecified subgroup analyses: We did not conduct the "treatment status" analysis (i.e. trials of stimulant-naïve participants versus trials of previously stimulant treated participants) since it was practically the same analysis as the withdrawal effects analysis. We did not consider the "publication status" analysis as feasible. We included data from various sources such as regulatory documents, data published on trial registry sites, and data sent directly from the investigators, which blurred the distinction between published and non-published data. We were unable to do our planned sensitivity analyses based on trials of overall 'low risk' of bias, since there were no trials rated 'low risk'.

Trial Sequential Analysis

In our protocol, we specified to run such analyses. We judged that this would be uninformative, since all trials were at high risk of bias and had limited generalisability.

RESULTS

Description of studies

Results of the search

Our first search (17 Oct 2017) returned 8,086 hits and we imported 4,324 records into Covidence after removal of duplicates. The updated search (15 March 2019) returned 684 records, and we imported 410 after removal of duplicates. An additional 27 records were manually added from the European Union Clinical Trial Register (EUCTR) and the ISRCTN trial registry. From these 4761 records, we full-text screened 243 and included 117. Our search of drug regulatory agency databases, pharmaceutical company databases, correspondence with trial authors and cross-references gave 55 additional records. In total, we included 172 records of published reports, drug regulatory documents, trial registry entries, and other documents, describing 25 randomised placebo-controlled trials (Figure 1). See Appendices regarding the regulatory documents (eTable 2), trial registries (eTable 3 - 5), pharmaceutical companies (eTable 6) and author correspondence (eTable 7).

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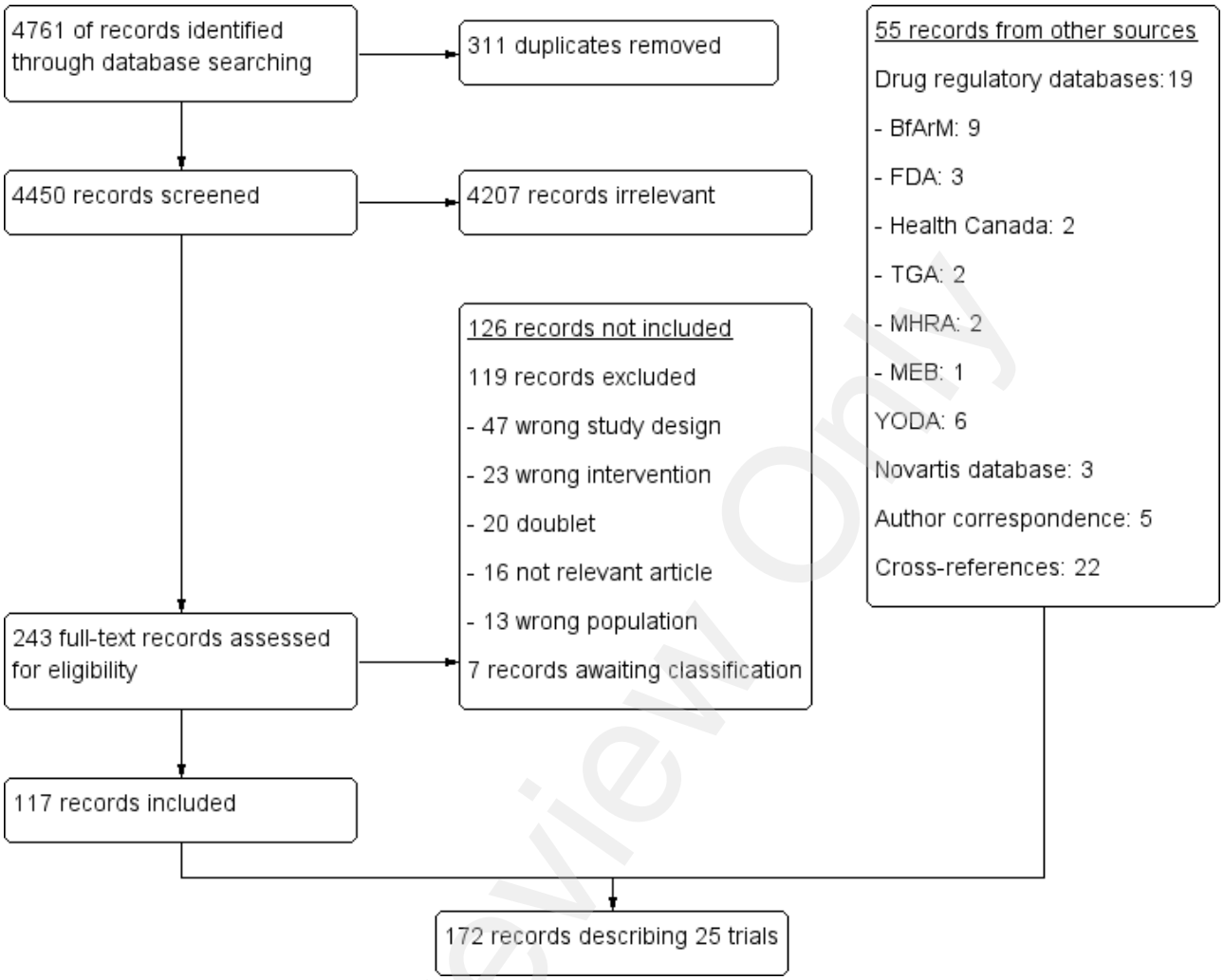
Figure 1. Flow diagram.



Included studies

We included 25 randomised, parallel-group, placebo-controlled trials (4,876 participants) of extended-release methylphenidate compared to placebo started between 1998 and 2016. Six different extended-release methylphenidate formulations were used in the trials and the median duration was 8 weeks (range 2 to 52 weeks). Twelve trials (3,836 participants, 79% of total sample) were industry-sponsored, four trials (708, 15%) were publicly funded with industry-involvement, eight trials (312, 6%) were publicly funded, and one (20 participants) had unclear funding. We included drug regulatory documents from eight trials (Spencer 2003, Rösler 2004, Medori 2005, Adler 2006, Casas 2008, Retz 2008, Huss 2010, Foquest 2014). Key trial characteristics are summarised in Table 1.

All trials compared extended-release methylphenidate with placebo. Levin 1998a included bupropion and Weisler 2009 included atomoxetine as active comparator. Twenty-one trials provided data for our review and four trials did not: College Study was never conducted, results from the Combine Substudy 2005 and Asherson 2016 were unpublished, and Methacan 2017 is presumably ongoing.

Setting and participants

Twenty-two trials had an outpatient setting and three trials were conducted in prison (Ginsberg 2007, Konstenius 2007, Asherson 2016). The industry trials were very homogenous in regard to setting, population and trial design. The five publicly funded trials that reported outcome data for this review either included participants with a comorbid substance abuse diagnosis (Levin 1998a, Levin 1998b, Konstenius 2006), was conducted in prison with inmates (Ginsberg 2007), or both (Konstenius 2007). We have summarised key trial setting and participant characteristics in table 2.

Table 1. Key trial characteristics

Trial	Formu-lation	Study start – study stop	Sponsor	Categorisation	No. par-	Dura-tion (weeks)

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					tici-pants	
Levin 1998a	SR MPH	Feb 1998 - Oct 2004	NIDA	Public trial	98[e]	10
Levin 1998b	SR MPH	April 1998 - Mar 2004	NIDA	Public trial	106	13
Levin 2001	SR MPH	Not described	Not described	Unclear	20	4
Biederman 2003	OROS MPH	June 2003 – Aug 2007	McNeil / Janssen	Industry trial	227	6
Spencer 2003	Dex-MPH ER	Apr 2003 - Sep 2003	Novartis	Industry trial	221	5
Chronis-Tuscano 2004	OROS MPH	Dec 2004 - Dec 2006	University of Maryland and McNeil	Public trial with industry-involvement[a]	20	2
Rösler 2004	ER MPH	Nov 2004 - May 2006	Medice	Industry trial	359	24
Combine Substudy 2005	SR MPH	Dec 2005 - Apr 2007 (est)	NIAAA	Public trial	No data	12
Medori 2005	OROS MPH	Apr 2005 - Aug 2006	Janssen	Industry trial	402	5
Winhusen 2005	OROS MPH	Nov 2005 - Mar 2008	NIDA	Public trial with industry-involvement[b]	255	11
Adler 2006	OROS MPH	Apr 2006 - Dec 2006	McNeil	Industry trial	229	7
Konstenius 2006	OROS MPH	Feb 2006 - Jun 2007	Addiction Centre Stockholm	Public trial	24	12
Compas 2007 (Compas 2007 CM, Compas 2007 GPT)	ER MPH	Apr 2007 - Aug 2011	German Federal Ministry of Education and Research	Public trial with industry-involvement[c]	433	52
Ginsberg 2007	OROS MPH	May 2007 - Apr 2010	Karolinska University Hospital	Public trial	30	5
Konstenius 2007	OROS MPH	Apr 2007 - Sep 2011	Addiction Centre Stockholm	Public trial	54	24
Casas 2008	OROS MPH	Feb 2008 - Apr 2009	Janssen	Industry trial	279	13
Retz 2008	ER MPH	Sep 2008 - Jan 2010	Medice	Industry trial	162	8
College Study 2009	OROS MPH	Not conducted	University of Pittsburgh	Public trial with industry-involvement[d]	Not conducted	8
Goodman 2009	OROS MPH	July 2009 - Feb 2010	Janssen	Industry trial	357	6

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Weisler 2009	OROS MPH	May 2009 - Jan 2010	Janssen	Industry trial	216[f]	6
Huss 2010	LA MPH	Nov 2010 - Aug 2012	Novartis	Industry trial	725	9
Takahashi 2011	OROS MPH	Mar 2011 - Apr 2012	Janssen	Industry trial	284	8
Foquest 2014	CR MPH	Oct 2014 - Jan 2015	Purdue	Industry trial	375	4
Asherson 2016	OROS MPH	May 2016 - Jul 2019	King's College London	Public trial	No data	8
Methacan 2017	LA MPH	Not described	Assistance Publique Hopitaux de Paris	Public trial	Ongoing	12

Table 1 legend. Listed in chronological order of study conduct. Abbreviations: CR= controlled-release, ER = extended-release, LA = Long-acting, MPH = methylphenidate, NIDA = National Institute on Drug Abuse, NIAAA = National Institute on Alcohol Abuse and Alcoholism, OROS = Osmotic-controlled Release Oral delivery System, SR = Sustained-release. A) According to ClinicalTrials.gov, the sponsor was University of Maryland and McNeil was a collaborator. According to the published report the trial was "supported by" McNeil. B) Janssen is listed as collaborator on ClinicalTrials.gov. c) Medice's medical director was involved in designing the trial and collecting data according to the published reports. D) Ortho-McNeil-Janssen listed as collaborator on ClinicalTrials.gov. e) Including the bupropion arm. F) Including the atomoxetine arm.

Trial ID	Location / no. sites	Mean age	Gender (% male)	Required substance abuse co-diagnosis	Other trial characteristics
Levin 1998a	US, 5 sites	39	57	Opiate dependency	All participants were maintained on a methadone program during the trial.
Levin 1998b	US, 2 sites	37	83	Cocaine dependency	None
Levin 2001	US, 1 site	37	63	No	None
Biederman 2003	US, 1 site	36	55	No	None
Spencer 2003	US, 18 sites	39	57	No	None
Chronis-Tuscano 2004	US, 1 site	40	0	No	All participants were mothers who had daughters also diagnosed with ADHD
Rösler 2004	Germany, 28 sites	35	50	No	None
Combine Substudy 2005	US, 1 site	No data	No data	Alcohol dependency	None
Medori 2005	13 European countries, 48 sites	34	54	No	None

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Winhusen 2005	US, 6 sites	38	57	No	All participants received a transdermal nicotine patch as part of a smoking cessation program
Adler 2006	US, 27 sites	39	56	No	None
Konstenius 2006	Sweden, 1 site	37	79	Amphetamine dependency	None
Compas 2007 (Compas 2007 CM, Compas 2007 GPT)	Germany, 7 sites	35	50	No	None
Ginsberg 2007	Sweden, 1 site	34	100	No	Conducted in a prison setting with male inmates
Konstenius 2007	Sweden, 1 site	42	100	Amphetamine dependency	Conducted in prison setting with male inmates. First two weeks of trial in prison before release, and remaining 22 weeks outside prison.
Casas 2008	Europe, 42 sites	36	52	No	None
Retz 2008	Germany, 11 sites	37	47	No	None
College Study 2009	US, 1 site	Not conducted	Not conducted	No	None
Goodman 2009	US, 35 sites	36	53	No	None
Weisler 2009	US, 37 sites	33	62	No	None
Huss 2010	(Belgium, Sweden, Denmark, Germany, Norway, Columbia, South Africa, USA, Singapore), 67 sites	35	55	No	None
Takahashi 2011	Japan, 39 sites	34	49	No	None
Foquest 2014	US and Canada, 38 sites	36	47	No	None
Asherson 2016	UK, 3 sites	No data	100	No	Conducted in a prison setting with male inmates
Methacan 2017	France, 2 sites	Ongoing	Ongoing	Cannabis dependence	None

Risk of bias in included studies

We assessed the risk of bias for the 21 studies reporting outcome data (Figure 2). See the individual assessments in the Characteristics of included studies.

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Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

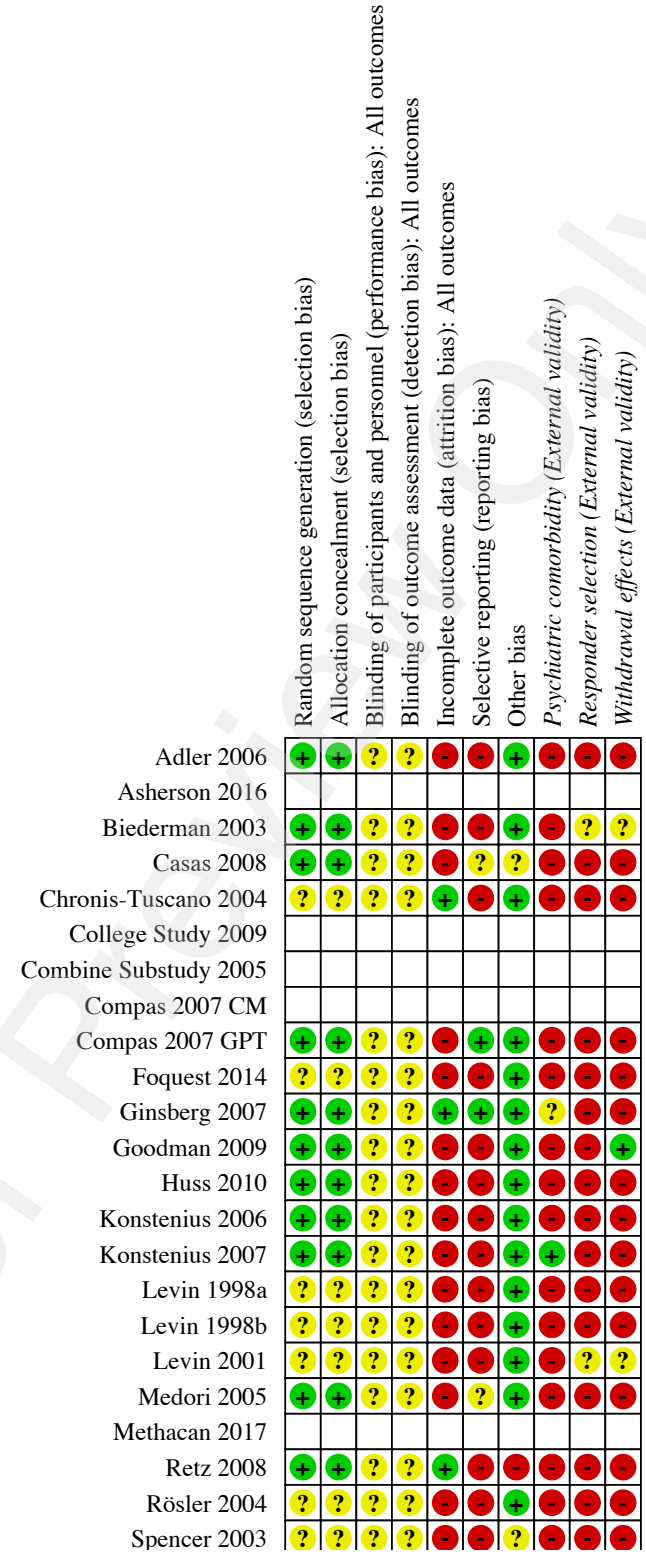

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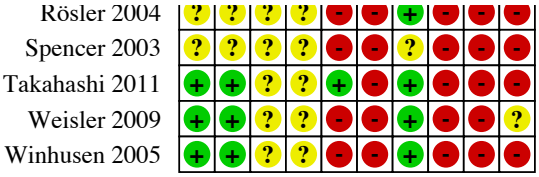
Figure 2. (Continued)



Allocation

Fourteen studies described adequate methods for randomisation and allocation concealment and seven studies reported insufficient information and were rated unclear.

Blinding

All 21 trials were rated at unclear risk of bias for blinding of participants and personnel and blinding of investigators. Fourteen trials employed a dose titration schedule and seven trials used a fixed dose trial design. One trial (Konstenius 2007)reported to test for unblinding. The trial used a dose titration design and tested whether the participants could guess their allocation during the titration phase. They reported that 48% of the participants in each group correctly guessed their allocation, 11% and 26% were wrong, and 41% and 26% were uncertain. Thus, the blinding was less than perfect. The remaining trials did not report whether they tested for unblinding.

Incomplete outcome data

Four trials were rated at low risk; Chronis-Tuscano 2004 lasted two weeks only, Ginsberg 2007 was conducted in a prison setting, and two industry-sponsored trials (Retz 2008, Takahashi 2011) had low dropout rates. Seventeen trials were rated as high risk with dropout rates ranging from 10% to 63% (methylphenidate) and 6% to 55% (placebo). Eleven of these trials carried the last observation forward.

Selective reporting

We rated two trials (Compas 2007 CM/Compas 2007 GPT and Ginsberg 2007) as having low risk of bias, two trials (Medori 2005, Casas 2008) as having unclear risk of bias and all other trials as having a high risk. Harms were particularly poorly reported. Nineteen trials reported on adverse events to various degrees, but we had access to the full lists without reporting thresholds for two trials only (Compas 2007 CM/Compas 2007 GPT and Ginsberg 2007). Adverse events reporting thresholds were prevalent also in drug regulatory documents, and thresholds varied for different documents describing the same trials.

Other potential sources of bias

We rated one trial (Retz 2008) as high risk due to baseline differences in gender distribution and self-rated symptom severity. We rated one trial (Spencer 2003) at unclear risk, since it was noted in the FDA review that an audt of trial sites had found a miscoding of a participant's reason to dropout out, which we could not judge the overall impact of. The remaining trials were rated low risk of bias.

Overall risk of bias assessment

We rated all 21 studies to have an overall high risk of bias. The blinding domains were rated as unclear for all trials, and we identified substantial biases in the attrition and selective outcome reporting domains.

Generalisability (external validity) assessment

All 21 trials were rated at high risk in at least one of the three external validity domains. Fifteen trials (4,046 participants, 83% of total sample) were rated at high risk in all three domains, of which nine were industry trials. See the individual assessments in the Characteristics of included studies.

Restrictive inclusion criteria

We rated one trial (Konstenius 2007) at low risk, one as unclear (Ginsberg 2007) and 19 trials at high risk due to restrictions of allowed psychiatric comorbidity. The limited external validity of the trials was acknowledged in several reports (Chronis-Tuscano 2004, Adler 2006, Compas 2007 CM, Casas 2008, Huss 2010, Takahashi 2011).

Responder selection ('Enriched design')

Two trials (Levin 2001, Biederman 2003) were rated unclear, and 19 trials were rated at high risk. Sixteen of these trials described how participants were excluded based on previous treatment response, e.g. due to a “history of poor response” (Spencer 2003), were “known non-responders” (Casas 2008) or “non-responsive” (Ginsberg 2007), and three trials (Chronis-Tuscano 2004, Rösler 2004 and Retz 2008) reported how many of the participants had previously been exposed to methylphenidate.

Withdrawal effects

We rated one trial (Goodman 2009) at low risk, since the inclusion criteria stipulated stimulant treatment was not allowed within five years of enrolment. We rated four trials at unclear risk, either due to a lack of information (Levin 2001, Biederman 2003, Weisler 2009) or a washout phase of 6 months (Compas 2007 CM/Compas 2007 GPT). We rated 16 trials at high risk, of which 14 stated a washout phase or stimulant-free period of 1 week (Levin 1998b), 1-2 weeks (Adler 2006), 1-4 weeks (Spencer 2003, Huss 2010, Takahashi 2011), 2 weeks (Levin 1998a, Rösler 2004, Konstenius 2006, Ginsberg 2007, Retz 2008, Konstenius 2007, Casas 2008) and 1 month (Medori 2005, Winhusen 2005), respectively. Two trials (Chronis-Tuscano 2004, Foquest 2014) did not specify the length of the washout period.

Effects of interventions

See: **Summary of findings 1** Extended-release methylphenidate compared to placebo for ADHD

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Comparison 1: Extended-release versus placebo

Twenty-one trials reported outcome data for this comparison.

Short term follow-up (up to 6 months)

Primary outcomes

Functional outcomes

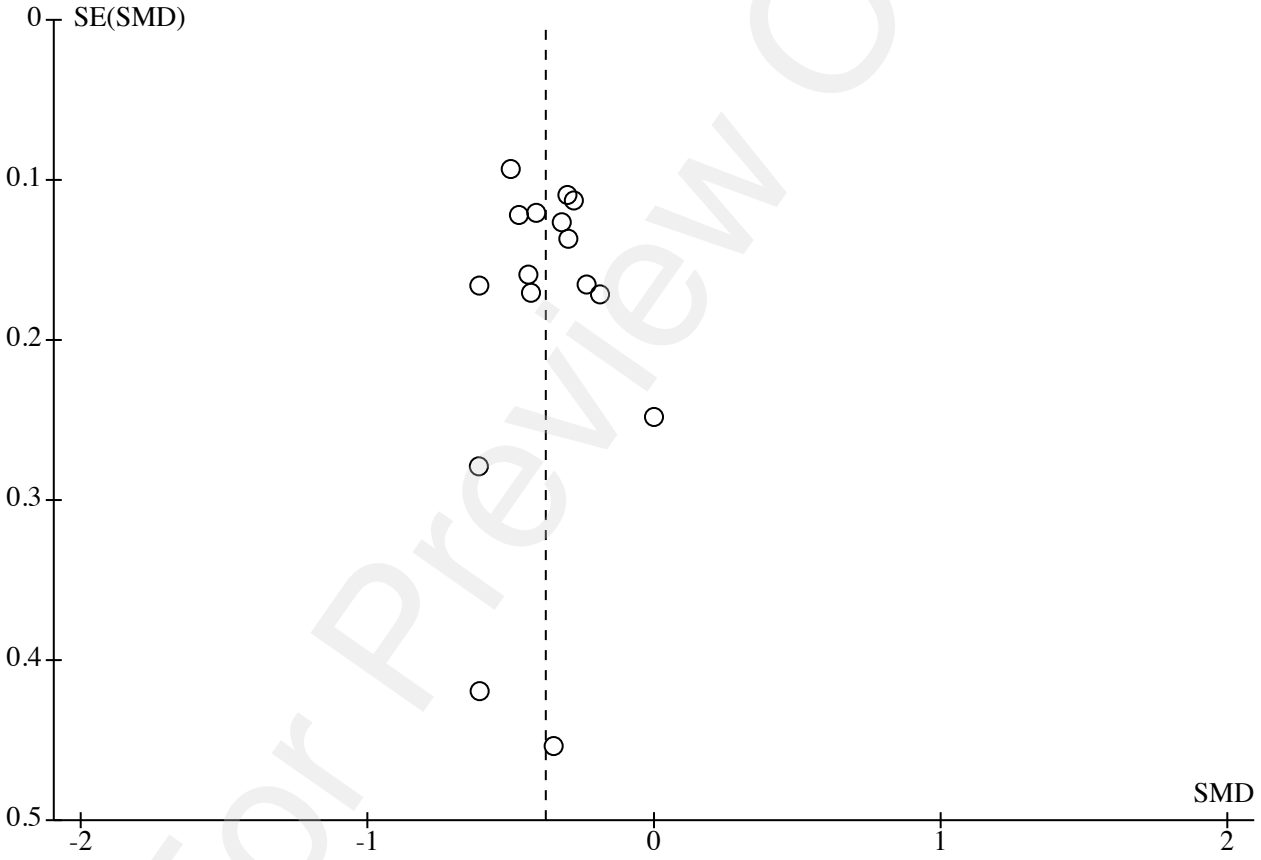
One trial (Compas 2007 CM/Compas 2007 GPT) reported a mean difference of 0.15 (95% CI: -1.81 to 2.11) days missed at work/ school/ training at 13 weeks of follow-up favouring methylphenidate (Analysis 1.1) and 0.4 days (95% CI: -1.6 to 2.5) between weeks 13 and 26 favouring methylphenidate (Analysis 5.1)

Three trials specified functional outcomes we could not analyse: College Study 2009 defined Grade Points Average (i.e. final grades for college students) but the trial was not conducted. Konstenius 2007 defined "relapse to crime" (e.g. readmission to prison) and Asherson 2016 prespecified "number of adjudications for antisocial behaviour" and "positive incentive and earned privileges" in prison but the outcomes were not reported.

Self-rated ADHD symptom severity

Fifteen trials (3,424 participants) showed an SMD of 0.38 (95% CI: 0.31 to 0.45), I^2 = 0%, in favour of methylphenidate (Analysis 1.2). The funnel plot was symmetrical (Figure 3). Ginsberg 2007 was a small study (n= 30) conducted in a prison setting, 60% of the participating inmates had a comorbid amphetamine substance abuse disorder. The trial reported an SMD of 1.6, which we considered to be an outlier and removed it from the meta-analysis, which did not change the overall result.

Figure 3. Funnel plot: Extended-release methylphenidate versus placebo: ADHD symptoms (self rated).



The mean difference was 3 points (95% CI: 1.76 to 4.34) on the most commonly used DSM-IV total ADHD 18-item scale (0-54 points) (Analysis 1.3).

Serious adverse events

Fourteen trials (4,078 participants) showed a risk ratio of 1.43 (CI 95% CI: 0.85 to 2.43), I^2 = 0%, with the point estimate in favour of placebo (Analysis 2.1). The funnel plot was symmetrical (Figure 4). See eTable 8 for the full list of events.

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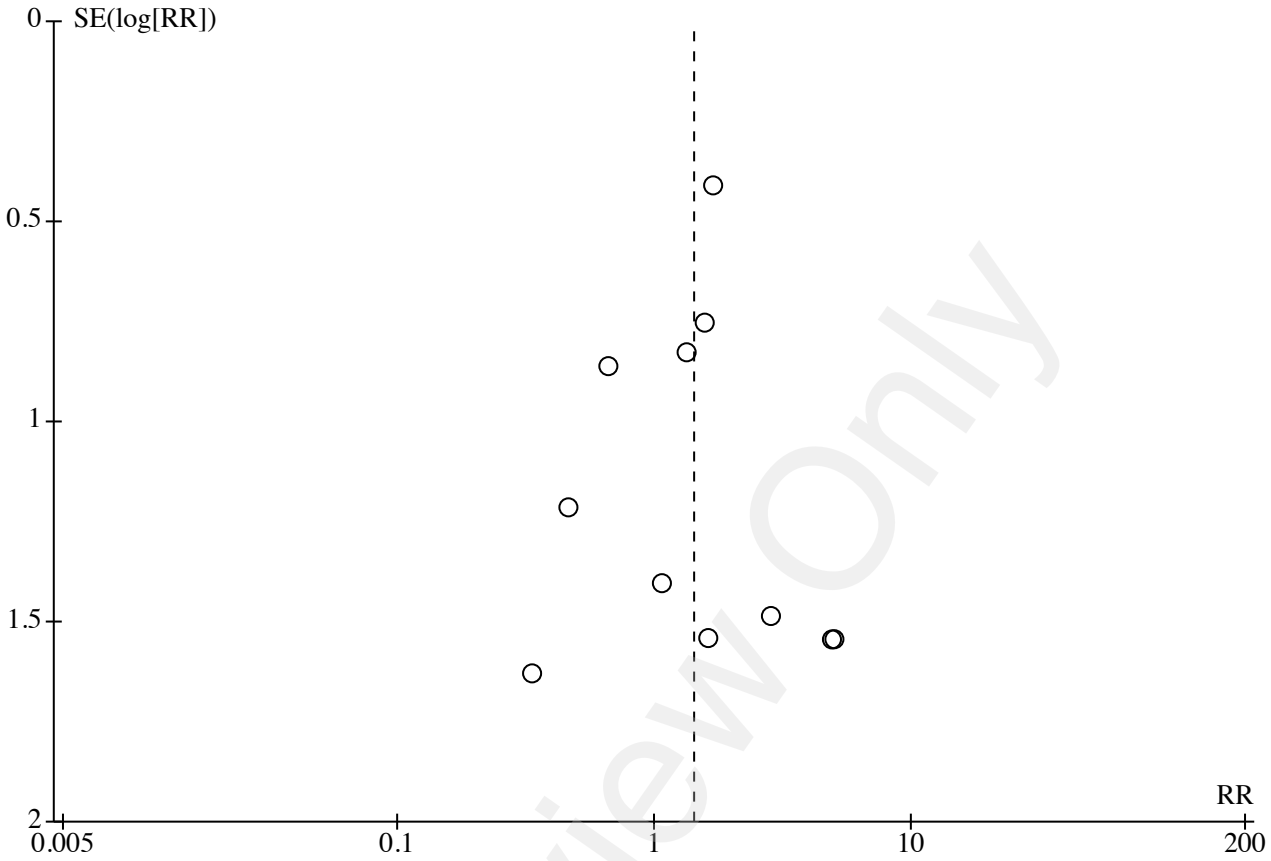
Figure 4. Funnel plot: Extended-release methylphenidate versus placebo: serious adverse events.



Secondary outcomes

Quality of life

Five trials (1,513 participants) showed an SMD of 0.12 (95% 0.01 to 0.22), I^2 = 0%, favouring methylphenidate (Analysis 1.4). Three studies did not report prespecified quality of life outcomes (Biederman 2003, Adler 2006, and Foquest 2014), Asherson 2016 is unpublished and Goodman 2009 reported subdomains on the AIM-A scale but not a total score.

The mean difference was 0.9 point (95% CI: -0.31 to 2.17) on the most commonly used Q-LES-QSF scale (range 14 - 70 points) (Analysis 1.5).

Investigator rated ADHD symptom severity

Twenty trials (4,213 participants) showed an SMD of 0.43 (95% CI: 0.35 to 0.51), I^2 = 27%, favouring methylphenidate (Analysis 1.7). The funnel plot was symmetrical (Figure 5).

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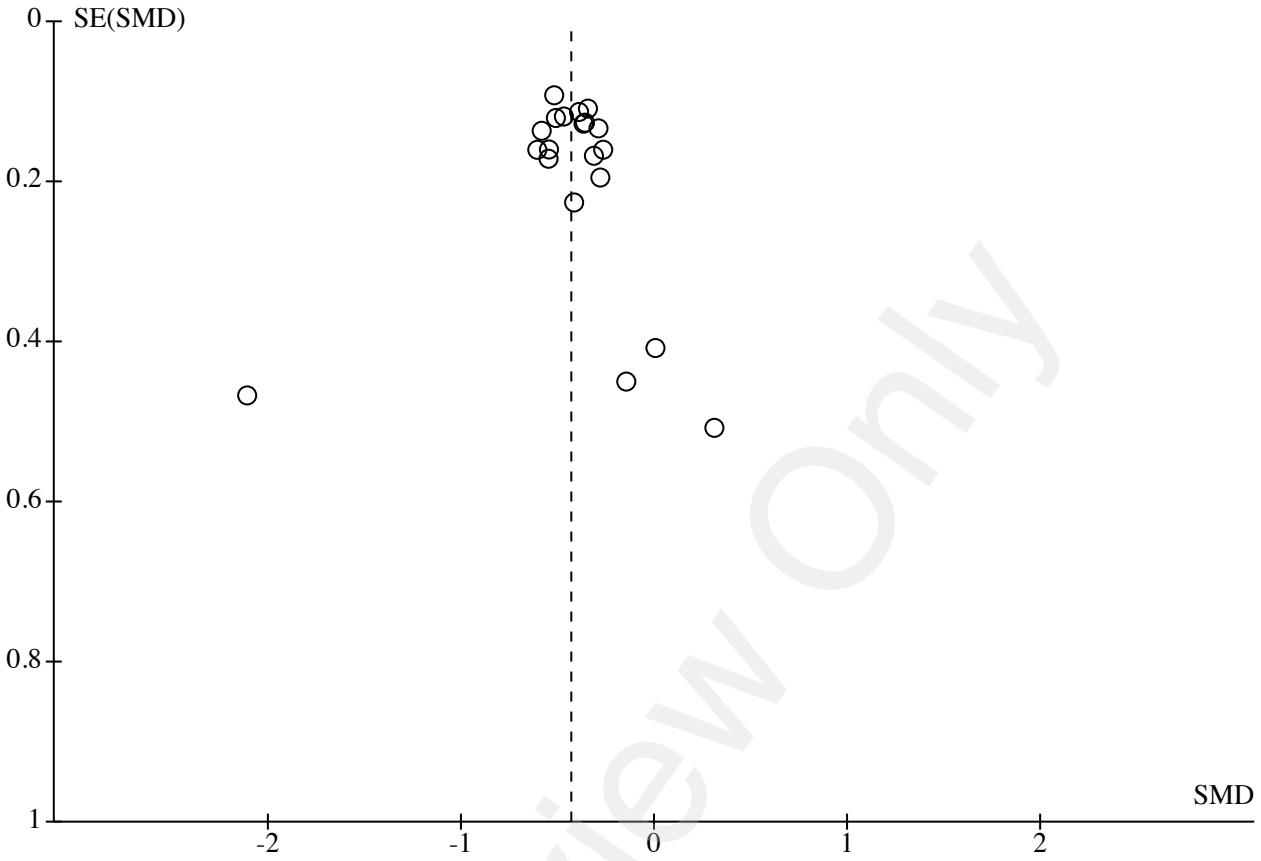
Figure 5. Funnel plot: Extended-release methylphenidate versus placebo: ADHD symptoms (investigator rated).



The mean difference was 5.35 points (95% CI: 3.97 to 6.73) on the most commonly used DSM-IV total ADHD 18-item rating scale (range 0-54 points) (Analysis 1.8).

Peer rated ADHD symptom severity

Two trials (630 participants) reported an SMD of 0.39 (95% CI: 0.22 to 0.57), I^2 = 0%, favouring methylphenidate (Analysis 1.9).

Severe psychiatric adverse events

The components of this outcome were inconsistently reported. We did not perform a meta-analysis due to scarcity and heterogeneity of data, but all available data are presented in eTable 9 to eTable 11.

Cardiovascular parametres

Ten trials (2,314 participants) showed a difference on pulse of 4.2 beats per minute (95% CI: 2.3 to 6.2), I^2 = 76%, higher for methylphenidate (Analysis 2.4). There were no differences between methylphenidate and placebo on systolic (Analysis 2.2) and diastolic blood pressure (Analysis 2.3).

Adverse events

For overall dropout (21 trials, 4,769 participants), RR = 1.01 (95% CI: 0.84 to 1.21), I^2 = 59% (Analysis 2.6). For dropouts due to adverse events (15 trials, 3,963 participants), RR = 2.36 (95% CI: 1.62 to 3.43), I^2 = 14%, favouring placebo (Analysis 2.7). For participants experiencing any adverse event (14 trials, 4,214 participants), RR = 1.27 (95% CI: 1.19 to 1.37), I^2 = 80%, favouring placebo (Analysis 2.8). For number of adverse events (two trials, 576 participants) reported on 1,667 events in 289 participants on methylphenidate and 1,139 events in 287 participants on placebo. For participants experiencing psychiatric adverse events (6 trials, 2,482 participants), RR = 1.99 (95% CI: 1.54 to 2.58), I^2= 57%, favouring placebo (Analysis 2.10). Weight was 1.8 kg (CI 95% CI: 1.1 to 2.3, I^2= 85%) lower for those on methylphenidate (Analysis 2.5).

We estimated risk ratios for 12 specific adverse effects (table 3). Ten events occurred more frequently for those on methylphenidate with risk ratios ranging from 1.35 (95%: 1.18 to 1.54) for headache to 5.52 (95%: CI 2.77 to 10.99) for feeling jittery. Two events (depression and irritability) did not occur more frequently for those on methylphenidate.

Table 3.

Adverse event	No. trials (population)	Risk ratio (95% CI)	I^2	Analysis

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Decreased appetite	16 trials (4491 participants)	4.08 (3.34 to 4.98)	0%	Analysis 2.11
Dry mouth	16 trials (4491 participants)	3.36 (2.61 to 4.34)	16%	Analysis 2.12
Headache	16 trials (4238 participants)	1.35 (1.18 to 1.54)	0%	Analysis 2.13
Palpitations	15 trials (4274 participants)	3.71 (2.52 to 5.46)	5%	Analysis 2.15
Insomnia	16 trials (4435 participants)	1.98 (1.51 to 2.57)	5%	Analysis 2.16
Sexual dysfunction	7 trials (3057 participants)	2.66 (1.31 to 5.39)	0%	Analysis 2.17
Anxiety	13 trials (3829 participants)	2.23 (1.40 to 3.57)	28%	Analysis 2.18
Depression	7 trials (2791 participants)	1.47 (0.87 to 2.49)	39%	Analysis 2.19
Irritability	11 trials (3377 participants)	1.39 (1.00 to 1.93)	0%	Analysis 2.20
Feeling jittery	7 trials (2254 participants)	5.52 (2.77 to 10.99)	0%	Analysis 2.21
Agitation	8 trials (3166 participants)	2.16 (1.25 to 3.71)	9%	Analysis 2.22
Aggression	4 trials (1319 participants)	2.10 (1.32 to 3.33)	0%	Analysis 2.23

Subgroup and sensitivity analyses

Six outcomes met our predefined threshold (I^2 above 50%) for making subgroup and sensitivity analyses. We considered it inappropriate to analyse four of these outcomes due to probable selective reporting: Pulse (Analysis 2.4) was reported by ten trials, diastolic blood pressure by nine (Analysis 2.3), body weight by eight, and 'participants experiencing psychiatric adverse events (Analysis 2.10) by six trials only.

For "overall dropout rates", the four subgroup analyses did not show any differences (Analysis 6.1 to Analysis 6.4) and we did not conduct the sensitivity analysis based on attrition bias. For "participants experiencing any adverse events", the "funding" subgroup analysis showed a higher proportion of participants experiencing adverse events in industry trials compared to publicly funded trials with industry-involvement (Analysis 6.8). There were no differences in the other analyses (Analysis 6.5, Analysis 6.7 and Analysis 6.9).

Medium term follow-up (up to 12 months)

One trial (Compas 2007 CM/Compas 2007 GPT) reported medium-term outcome data at 52 weeks. Due to large dropout rates at 52 weeks, we used completers' data as the primary analyses and last mean carried forward data as the secondary analyses.

Primary outcomes

Functional outcomes

The mean difference was 0.7 days (95% CI: -1.6 to 3.0) of missed days from work/ school/ training favouring placebo between week 26 and 52 (Analysis 5.2). We asked the corresponding author for baseline to week 52 data, but did not receive the data.

Self-rated ADHD symptoms

The mean difference was 1.59 point (95% CI: -1.09 to 4.26), I^2= 20%, on the DSM-IV total ADHD scale (range 0 to 54 points), using completers' data (Analysis 5.3) and 2.23 points (95% CI: 0.95 to 3.50), I^2 = 2%, on the ADHD Index (range 0 to 36 points) using the last mean carried forward data (Analysis 5.4)

Secondary outcomes

Investigator rated ADHD symptoms

The mean difference was 1.29 point (95% CI: -0.8 to 3.38), I^2= 20%, on the DSM-IV total ADHD rating scale (0 to 54 points), using completer's data (Analysis 5.5) and 2.18 points (95% CI: 0.80 to 3.55), I^2= 15%, on the ADHD Index (range 0 to 36 points), using the last mean carried forward data (Analysis 5.6).

Quality of life

The mean difference was 0.66 points (95% CI: -1.64 to 2.97), I^2 = 36% (Analysis 5.7).

Serious adverse events and other harms

See under short-term follow-up.

Long-term follow-up (more than 12 months)

There were no trials with a continuous randomised, placebo-controlled phase of more than 52 weeks.

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Certainty of the evidence

We rated the certainty of the evidence for all outcomes as 'very low' due to 'high risk of bias' and 'indirectness'. Several trial design characteristics contributed to the "indirectness" including exclusion of participants with psychiatric comorbidity, responder selection and withdrawal effects (see also (Assessment of risk of bias in included studies), and short trial duration.

Comparison 2: Extended-release methylphenidate versus atomoxetine

One trial (Weisler 2009) compared OROS methylphenidate 54 mg per day and atomoxetine 80 mg per day. There were insignificant differences for most reported outcomes, except initial insomnia and weight change, which favoured atomoxetine (Analysis 3.1 to Analysis 3.15).

Comparison 3: Extended-release methylphenidate versus bupropion

One trial (Levin 1998a) compared sustained-release methylphenidate and bupropion 400 mg per day. There were no reported differences on overall dropout rates, dropouts due to adverse events, and investigator rated ADHD symptoms (Analysis 4.1 to Analysis 4.3)

DISCUSSION

Summary of main results

We included 25 clinical trials using six different extended-release methylphenidate formulations for adults with ADHD. Twenty-one trials reported data of which 12 were industry-sponsored.

The reported beneficial effects of methylphenidate over placebo on symptom rating scales were small to moderate, the effects on quality of life were negligible, and there were no effects on days missed at work. We found no increase in the risk of serious adverse events, or overall dropout, whereas the risk of experiencing any adverse event, dropping out due to an adverse event, or the risk of experiencing any psychiatric adverse event were higher on methylphenidate. The risk ratios for all but two assessed adverse events were higher for methylphenidate than placebo, including headache, dry mouth, palpitations and psychiatric adverse events such as anxiety, agitation, and feeling jittery. All trials were rated at high risk of bias, the mean trial duration was eight weeks only, and we identified important limitations regarding the generalisability of the results.

Overall completeness and applicability of evidence

We searched drug regulatory agency databases and included more than 1,100 pages of regulatory documents from drug approval reviews, public assessment reports, and other documents. Despite these efforts, our results are seriously limited by selective reporting. Important patient relevant outcomes were not reported in a number of the included trials: 14 (67%) of 21 trials reported on serious adverse events, 10 (48%) reported on cardiovascular variables, five of 10 trials (50%) reported on prespecified quality of life outcomes, and only one (5%) reported on functional outcomes. Additionally, only seven of our 23 author correspondences resulted in more data to include (eTable 6).

We have doubts about the rates of important psychiatric harms. In the British drug regulator's (MHRA) OROS-methylphenidate public asessment report, we noted that "psychosis/ mania" was reported to occur in 3% of participants on methylphenidate versus 1% in the placebo group during the double-blind placebo-controlled phase (MHRA 2010, p. 63). This estimate, based on three pivotal trials (Medori 2005, Adler 2006, Casas 2008), is 30 times higher than the 0.1% risk of "new psychotic or manic symptoms" according to FDA's Prescribing Information (FDA 2017, section 5.2). We also noted large differences across trials that were not explained by obvious trial differences. For example, Rösler 2004 reported that 11% on methylphenidate experienced 'reduced libido' compared to 1% in the pooled analysis of Medori 2005, Adler 2006, and Casas 2008 (MHRA 2010, p. 61). The Dutch drug regulatory agency, MEB, noted in their public assessment report of long-acting methylphenidate (which they did not approve for market authorisation) that the strict exclusion criteria probably reduced the incidence of reported harms in the trials, "*Psychiatric AEs were common (i.e. total of 43%, including insomnia 11%, anxiety 7%, irritability 7%, and restlessness 7%) and some were serious. Since these events were more common in patients with a psychiatric history and since elaborate psychiatric exclusion criteria were implemented in the study, which prevented inclusion of patients with more serious psychiatric comorbidity, it is concluded that the rate of psychiatric AEs would have been even higher without these exclusions*" (MEB 2016, p. 36).

We have limited knowledge of minimal important differences on ADHD symptom rating scales. For the quality of life outcome, Q-LES-QSF, we found a difference of 1 point (range 14 to 70 points), whereas the minimal important difference is estimated to be 3 points (Mick 2008).

Quality of the evidence

We rated the overall certainty of the evidence as "very low", due to high risk of bias and limitations related to external validity, which means that further research is likely to change the effect estimates. The statistical heterogeneity was low for most effect estimates, which was unsurprising since the majority of participants were enrolled in homogenous industry-sponsored trials.

A major limitation of the evidence is the limited generalisability due to several problematic trial design characteristics (exclusion of psychiatric comorbidity, responder selection, and withdrawal effects), short trial durations, high dropout rates, and a lack of patient-relevant outcomes. The MHRA found in their public assessment report (MHRA 2010) on OROS methylphenidate found that, "Current Psychiatric morbidity and a history of Psychiatric Morbidity appeared to reduce the effect size (excluding the 72mg dose in Study 3013. No obvious pattern of differences was seen in whether the adult was MPH naïve or not" (MHRA 2010, p. 51). However, to properly address the impact of such study designs, we would need access to clinical study reports and individual patient data, but ideally new and less biased trials should be conducted.

Potential biases in the review process

The major limitation is the high risk of selective outcome reporting due to a lack of access to trial protocols and clinical data. We asked Medice, the Marketing Authorisation Holder of Medikinet in Europe, for access to trial data from their two pivotal trials (Rösler 2004 and Retz 2008) in 2016. Medice's medical director declined our request with the argument that Cochrane reviews are "full

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of errors and biased" and then cited an article (Banaschewski 2016) criticising a Cochrane review of methylphenidate for children and adolescents with ADHD (Storebø 2015). In 2019, we asked the German drug regulatory agency, Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) about access to the same trial data. The agency consulted with Medice, which again declined the request. We plan to raise this rejection with the Heads of Medicines Agency, since European drug regulators are obliged to share clinical trial data (Gøtzsche 2011, Dyer 2020, CURIA 2020).

There are other biases and limitations in the review. The composite "severe psychiatric adverse event" outcome was not well suited to estimate psychiatric harms, and one should always be careful with composite outcomes. It was a limitation that we did not specify which adverse events to assess at the protocol stage. For future reviews of psychiatric drugs, we recommend prespecifying individual harms, preferably in collaboration with patients. It would also be preferable to pool adverse events according to their Medical Dictionary for Regulatory Activities (MedDRA) terms, rather than analysing individual events. Miscoding and splitting up events into separate terms may dilute potential signals of harms and make the analyses unreliable (Maund 2014).

Agreements and disagreements with other studies or reviews

Our results for adverse effects, cardiovascular effects and weight changes correspond with previous systematic reviews (Mick 2013, Storebø 2015, Liang 2018, Storebø 2018). Our quality assessment also agrees with Cochrane reviews on methylphenidate for ADHD in children and adolescents (Storebø 2015, Storebø 2018), amphetamines for ADHD in children and adolescents (Punja 2016) and adults (Castells 2018). It is difficult to compare our results directly with non-Cochrane reviews on methylphenidate for adult ADHD (Faraone 2004, Peterson 2008, Koesters 2009, Meszaros 2009, Faraone 2010, Castells 2011, Castells 2013, Cunill 2016, Cortese 2018). These reviews used different methodologies and included different drugs and trials. The most recent systematic review (Cortese 2018) reported similar effects on ADHD symptom scales, dropout rates due to adverse events, and overall dropout rates for methylphenidate. However, the review did not assess functional outcomes, quality of life, or individual adverse events and they rated the certainty for some of the outcomes as 'moderate' (clinician rated ADHD symptoms) or 'high' quality (dropout due to adverse events), whereas we rated the certainty of the evidence as 'very low' for all outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

Clinical guidelines and consensus documents, such as the European Consensus Statement (Kooij 2019) and the NICE guideline (NICE 2018), should reflect the 'very low' certainty of the evidence. The evidence to support methylphenidate as a pharmacological treatment for ADHD in adults is weak and treatment beyond 52 weeks is unsupported by randomised trials. In practice, each patient should make a shared decision with the healthcare professional and family and decide whether the reported benefits outweigh the harms for them.

Implications for research

It seems needed with well-conducted, long-term trials with drug naïve-participants measuring patient-relevant outcomes of extended-release methylphenidate for adult ADHD.

ACKNOWLEDGEMENTS

This protocol was produced within the Cochrane Developmental, Psychosocial and Learning Problems Review Group.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by year]

Levin 1998a

Study characteristics	
Methods	**Trial ID(s)**: NCT00061087, R01DA011444, NIDA-011444-1, 4184R **Trial registry entry**: https://clinicaltrials.gov/show/NCT00061087. **Sponsor**: New York State Psychiatric Institute **Funding/industry-involvement**: National Institute of Drug Abuse (NIDA) grants R01 DA00144, KO2 00465 and K02 DA00288. **Setting:** USA. **No. sites**: 5. **Start - completion**: Feb 1998 - March 2004. **Duration**: 10 weeks. **Sample size**: 65.
Participants	*Information on exclusion criteria related to psychiatric comorbidity is listed in the risk of bias table.* **ADHD diagnostic system**: DSM IV **Concomitant substance abuse disorder**: DSM IV: Opiate dependency **Mean age (range)**: 39 (Range: 18-60, inclusion criteria) **Males** (%): 57
Interventions	**Trial arms:** 1. Methylphenidate sustained-release (n= 32) 2. Bupropion sustained-release (n= 33) 3. Placebo (n= 33) **Type of methylphenidate**: Methylphenidate sustained release (SR) **Dosage**: 40 mg to 80 mg **Fixed or titrated**: Titrated **Administrations per day**: 2 **Co-intervention(s):** Weekly cognitive behavioural therapy + Methadone treatment program

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Levin 1998a *(Continued)*

Outcomes	*Reported outcome of relevance for the review. Missing outcomes are listed in the risk of bias domain "selective reporting".* 1. Adult ADHD Rating Scale (AARS) (self-rated, 18 items, 0-54 points) 2. Wender–Reimherr Adult Attention Deficit Disorder Scale (WRAADDS) (investigator-rated, 7 items, range not reported) 3. Dropouts due to adverse events
Notes	**Declared conflicts of interest**: "Dr. Levin is a consultant for Eli Lily and Company, Shire Pharmaceuticals Group, and Ortho-McNeil Pharmaceutical Inc. Also she has investigator-initiated grants with Eli Lily and Company and UCB Pharma Inc" (Levin 2006).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	1. "Randomization was stratified by site, and by the amount of recent cocaine use (no use, low use as defined as <10 days/month and $200/month spent, and high use as defined as ≥10 days/month and $200/month spent). Within each site, patients were stratified by gender and ethnicity" (Levin 2006).
Allocation concealment (selection bias)	Unclear risk	1. Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	1. "double-blind, placebo-controlled, randomized, three-arm trial" (Levin 2006). 2. "Folic acid in the form of a 1mg tablet was added to all placebo capsules in an attempt to improve the blind" (Levin 2006). 3. Stated, not tested.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	1. "double-blind, placebo-controlled, randomized, three-arm trial" (Levin 2006). 2. "Folic acid in the form of a 1mg tablet was added to all placebo capsules in an attempt to improve the blind" (Levin 2006). 3. Stated, not tested.
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Dropout rates: methylphenidate 11 of 32 (34 %) and placebo 8 of 33 (24 %). 2. 18 out of the 115 participants entered the study but did not complete the 2 week placebo lead-in (p. 141). 3. Dropouts due to adverse events: methylphenidate 1 of 11, placebo 2 of 8. 4. Statistical method to account for missing data: generalized estimation equation model (assumes missing data is random).
Selective reporting (reporting bias)	High risk	1. Adverse event reporting threshold: No threshold, but no systematic reporting of events. 2. Serious adverse events not reported (we assume none occured, but it was not described) 3. The WRAADS outcome was not reported, "no treatment effects" (Levin 2006, p. 144). 4. Blood pressure and pulse (Levin 2006, p. 139) not reported.
Other bias	Low risk	None found
Psychiatric comorbidity (External validity)	High risk	1. "Participants were excluded if they (1) met DSM-IV criteria for current psychiatric disorders (other than ADHD or substance abuse) which required psychiatric intervention or had a history of an eating disorder" (Levin 2006).

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Levin 1998a *(Continued)*

Responder selection (External validity)	High risk	1. "Patients with known sensitivity to MPH or BPR" (CT.gov).
Withdrawal effects (External validity)	High risk	1. "Participants were excluded if they […] were taking any prescription psychotropic medications other than methadone" (Levin 2006). 2. "Following 2 weeks of placebo lead-in, participants were randomized into one of the three arms. 3. 18 of the 115 participants entered the study but did not complete the placebo lead-in phase. 4. Current cocaine substance abuse was prevalent: methylphenidate group (64 %) and placebo (41 %).

Levin 1998b

Study characteristics	
Methods	**Trial ID(s)**: NCT00136734, 3236-NIDA-011755-1, R01DA011755. **Trial registry entry**: https://clinicaltrials.gov/show/NCT00136734 **Sponsor**: New York State Psychiatric Institute **Funding/industry-involvement**: National Institute on Drug Abuse (NIDA) grants: K23 DA16743, K23 DA00429, K02 DA00288, RO1 DA11755, and K02 DA00465. **Country:** USA. **No. sites:** 2. **Start - completion**: April 1998 - Mar 2004 **Duration:** 13 weeks. **Sample size**: 106 participants.
Participants	*Information on exclusion criteria related to psychiatric comorbidity is listed in the risk of bias table.* **ADHD diagnostic system**: DSM IV **Concomitant substance abuse disorder**: DSM IV: Cocaine dependence. **Mean age (range)**: 37 (Range: 23-52) **Males** (%): 83.
Interventions	**Trial arms:** 1. Methylphenidate sustained-release (n= 53) 2. Placebo (n= 53) **Type of methylphenidate**: Methylphenidate sustained-release (SR) **Dosage**: 40 mg to 60 mg **Fixed or titrated**: Titrated **Administrations per day**: 2 **Co-intervention(s):** Weekly cognitive behavioural therapy.
Outcomes	*Relevant outcomes are listed here.* 1. Adult ADHD Rating Scale (AARS) (self-rated, 18 items, 0-54 points) 2. Targeted Adult Attention Deficit Disorder Scale (TAADS) (7 Items, 0-28 points, investigator-rated)

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Levin 1998b *(Continued)*

	3. Dropouts due to adverse events
Notes	**Declared conflicts of interest**: "Dr. Levin is a consultant for Eli Lily and Company, Shire Pharmaceuti- cals Group, AstraZeneca, Cephalon/Alkermes and OrthoMcNeil Pharmaceutical Inc. Also she has research support from Eli Lily and Company, UCB Pharma Inc, Shire Pharmaceuticals Group, AstraZeneca and OrthoMcNeil Pharmaceutical Inc" (Levin 2007).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	1. "Participants were randomized into either the MPH or PBO group" (Levin 2007).
Allocation concealment (selection bias)	Unclear risk	1. Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	1. "This study was a double-blind, placebo-controlled, randomized trial" (Levin 2007). 2. "Folic acid in the form of a 1 mg tablet was added to all placebo capsules in an attempt to improve the double-blind" (Levin 2007). 3. Stated, not tested.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	1. "This study was a double-blind, placebo-controlled, randomized trial" (Levin 2007). 2. "Folic acid in the form of a 1 mg tablet was added to all placebo capsules in an attempt to improve the double-blind" (Levin 2007). 3. Stated not tested.
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Dropout rates: methylphenidate 30 of 53 (57 %), placebo 29 of 53 (55 %). 2. Dropouts due to adverse events: 1 of 30 and 1 of 29 respectively. We note that the majority of dropots were labelled "not interested". 3. Statistical method to account for missing data: General estimation equation method.
Selective reporting (reporting bias)	High risk	1. Adverse event reporting threshold: No specific threshold, but no systematic reporting. 2. Serious adverse events not described. We anticipate that no SAEs occured, but it is not reported. 3. AARS end point values not reported, there was "no significant difference between the groups" (Levin 2007). 4. Cardiovascular parametres not reported, although stated to be measured (p. 21).
Other bias	Low risk	None found
Psychiatric comorbidity (External validity)	High risk	1. "Participants were excluded if they (1) met DSM- IV criteria for current psychiatric disorders (other than ADHD or substance abuse) which required psychiatric intervention" (Levin 2007)
Responder selection (External validity)	High risk	1. "Known sensitivity to MPH" (Levin 2007). 2. "[Inclusion criteria] Meets DSM-IV criteria for cocaine dependence" (CT.gov)". 3. "Following the PBO lead-in phase, participants were randomized into either the MPH or PBO group" (Levin 2007). 4. 18 participants dropped out after entering the trial but before being randomised (figure 1).

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Levin 1998b *(Continued)*

Withdrawal effects (External validity)	High risk	1. "[Inclusion criteria] Meets DSM-IV criteria for cocaine dependence" (CT.gov). 2. The study contained a one-week placebo lead-in before being randomised to active drug or placebo.

Levin 2001

Study characteristics	
Methods	**Trial ID(s)**: Not registered. **Trial registry entry:** Not registered. **Sponsor**: Not reported. **Funding/industry-involvement**: Not reported. **Setting:** USA. **No. sites**: 1 site. **Start - completion**: Not reported **Duration**: 4 weeks **Sample size**: 20 participants
Participants	**ADHD diagnostic system**: DSM-IV. **Concomitant substance abuse disorder**: None **Mean age (range)**: 37 years (19 to 56). **Males** (%): 63. *Information on exclusion criteria related to psychiatric comorbidity is listed in the risk of bias table.*
Interventions	**Trial arms:** 1. Methylphenidate SR + placebo patch (n= 10) 2. Placebo + placebo patch (n= 10) 3. Methylphenidate SR + nicotine patch (not included in review) 4. Placebo + nicotine patch (not included in review) **Type of methylphenidate**: Methylphenidate sustained-release (MPH SR). **Dosage**: 20 mg. **Fixed or titrated**: Fixed. **Administrations per day**: 1. **Co-intervention(s)**: Not described.
Outcomes	*Reported outcome of relevance for the review. Missing outcomes are listed in the risk of bias domain "selective reporting".* 1. Clinical Global Impression Severity
Notes	**Declared conflicts of interest**: Not reported in Levin 2001.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

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Levin 2001 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	1. "The treatments were given in a randomized, double-blind fashion with a placebo patch and pill" (Levin 2001).
Allocation concealment (selection bias)	Unclear risk	1. "The treatments were given in a randomized, double-blind fashion with a placebo patch and pill" (Levin 2001).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	1. "The treatments were given in a randomized, double-blind fashion with a placebo patch and pill, whereby neither the participants nor the experimenters who worked with the participants were informed as to the treatment condition" (Levin 2001). 2. Stated, not tested.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	1. "The treatments were given in a randomized, double-blind fashion with a placebo patch and pill, whereby neither the participants nor the experimenters who worked with the participants were informed as to the treatment condition" (Levin 2001). 2. "ADHD symptoms were assessed by a clinician blind to treatment in a structured interview using the CGI scale" (Levin 2001). 3. Stated, not tested
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Dropout rates: methylphenidate 1 of 10 (10 %), placebo 3 of 10 (30 %). 2. Adverse events leading to dropouts: not described. 3. Statistical method used to account for missing data: not described.
Selective reporting (reporting bias)	High risk	1. Adverse events not reported. 2. Serious adverse events not reported.
Other bias	Low risk	None identified.
Psychiatric comorbidity (External validity)	High risk	1. "Participants with diagnoses of major depressive disorder or generalized anxiety disorder were excluded" (Levin 2001). 2. "All Ham-D scores of participants were 9 or lower" (Levin 2001).
Responder selection (External validity)	Unclear risk	1. "None of the participants were on methylphenidate or other stimulant medication before the study" (Levin 2001). 2. It is unclear if the participants were stimulant naïve or not.
Withdrawal effects (External validity)	Unclear risk	1. "None of the participants were on methylphenidate or other stimulant medication before the study" (Levin 2001). 2. Washout not described, and uncertain if the participants had to stop current medication and whether they were stimulant naïve or not.

Biederman 2003

Study characteristics	
Methods	**Trial ID(s)**: NCT00181571, 2003-p-000037 (protocol). **Trial registry entry**: https://clinicaltrials.gov/ct2/show/NCT00181571. **Sponsor**: Massachusetts General Hospital **Funding/industry involvement**: Ortho-McNeil Janssen ("Clinical trials were supported with financial support from Ortho-McNeil Janssen", Biederman 2010, and on ClinicalTrials.gov the company is listed as collaborator) **Setting**: United States **No. sites**: 1 site.

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Biederman 2003 *(Continued)*

	Start - completion: Jun 2003 - Aug 2007. **Duration**: 6 weeks. **Sample size**: 227 participants.
Participants	*Information on exclusion criteria related to psychiatric comorbidity is listed in the risk of bias table.* **ADHD diagnostic system**: DSM IV. **Concomitant substance abuse diagnosis**: No. **Mean age (range)**: 36 years (19-60) **Males** (%): 55.
Interventions	**Trial arms**: 1. OROS methylphenidate (n= 112) 2. Placebo (n= 115) **Type of methylphenidate**: OROS methylphenidate. **Dosage range**: 36 mg to 144 mg. **Fixed or titrated**: Titrated. **Administrations per day**: 1. **Co-intervention(s)**: Not described.
Outcomes	*Relevant outcomes are listed here.* 1. Adult ADHD Investigator System Report Scale (AISRS) (investigator-rated, 18 items, 0-54 points) 2. Cardiovascular variables 3. Harms
Notes	**Declared conflicts of interest**: "Dr Joseph Biederman is currently receiving research sup- port from the following sources: Alza, AstraZeneca, Bristol- Myers Squibb, Eli Lilly & Company, Janssen Pharmaceuticals Inc, McNeil, Merck, Organon, Otsuka, Shire, National Institutes of Mental Health and NICHD. In 2009, Dr Joseph Biederman received a speaker's fee from the following sources: Fundacion Areces, Medice Pharmaceuticals, and the Spanish Child Psy- chiatry Association. In previous years, Dr Joseph Biederman received research support, consultation fees, or speaker's fees for/from the following additional sources: Abbott, AstraZeneca, Celltech, Cephalon, Eli Lilly & Company, Esai, Forest, Glaxo, Gliatech, Janssen, McNeil, NARSAD, NIDA, New River, Novartis, Noven, Neurosearch, Pfizer, Pharmacia, The Prechter Foundation, Shire, The Stanley Foundation, UCB Pharma, Inc, and Wyeth. Dr Eric Mick receives research support from the following sources: Ortho-McNeil Janssen Scientific Affairs, Pfizer, Shire Pharmaceuticals; and has been an advisory board member for Shire Pharmaceuticals. Dr Surman has received research support from Abbott, Alza, Cephalon, Elminda, Eli Lilly, the Hilda and Preston Davis Foundation, McNeil, Merck, New River, National Institutes of Health, Organon, Pfizer, Shire, and Takeda; has been a speaker for Janssen-Ortho, McNeil, Novartis, and Shire; and has been a consultant/advisor for McNeil, Shire and Takeda. He has also been a speaker for the MGH Academy and Reed Medical Education, which produces programs that are funded by sev- eral pharmaceutical companies. Dr Robert Doyle has received speaker honoraria from Shire, Novartis, McNeil, Neuroscience Educational Institute, Continuing Medical Education Outfitters, PriMed, APA, and AACAP. Dr Hammerness has participated, as an investigator, in research studies funded by the following companies: Abbott, Bristol-Myers Squibb, Cephalon, Eli Lilly, Glaxo-SmithKline, Johnson & Johnson, McNeil, Merck, New River, Organon, Pfizer, Shire, and Takeda. In the past 2 years, Dr Hammerness has received research funds or participated in CME activities/professional talks supported by the following compa- nies: Abbott, Eli Lilly, Forest, McNeil, Shire. Dr Hammerness has also received research funds from Elminda Ltd and has par- ticipated in speaker training with Shire. Dr Hammerness has also received honoraria from Reed Medical Education (a com- pany working as a logistics collaborator for the MGH Psychia- try Academy); education programs supported through grants from pharmaceutical companies along with participant tuition. Ms Meghan Kotarski reports no competing interests. Dr Thomas Spencer has received research support from the following sources: Shire Laboratories Inc, Cephalon, Eli Lilly & Company,

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Biederman 2003 *(Continued)*

Glaxo- Smith Kline, Janssen, McNeil Pharmaceutical, Novartis Phar- maceuticals, Pfizer, and NIMH. Dr Thomas Spencer has been a speaker for the following speaker's bureaus: Shire Laboratories, Inc, Eli Lilly & Company, Glaxo-Smith Kline, Janssen, McNeil Pharmaceutical, and Novartis Pharmaceuticals. Dr Thomas Spencer has been on the advisory board for the following phar- maceutical companies: Shire Laboratories Inc, Cephalon, Eli Lilly & Company, Glaxo-Smith Kline, Janssen, McNeil Pharmaceutical, Novartis Pharmaceuticals, and Pfizer" (Biederman 2010).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	1. "All study subject randomizations and study medications were administered by the research pharmacy at the Massachusetts General Hospital" (Biederman 2010).
Allocation concealment (selection bias)	Low risk	1. "All study subject randomizations and study medications were administered by the research pharmacy at the Massachusetts General Hospital, and all doses of OROS- MPH and placebo were delivered in identically appearing tablets" (Biederman 2010).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	1. "Physician raters and subjects were equally blind to treatment assignment" (Biederman 2010). 2. "All study subject randomizations and study medications were administered by the research pharmacy at the Massachusetts General Hospital, and all doses of OROS- MPH and placebo were delivered in identically appearing tablets" (Biederman 2010). 3. Stated, not tested.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	1. "Physician raters and subjects were equally blind to treatment assignment" (Biederman 2010). 2. "All study subject randomizations and study medications were administered by the research pharmacy at the Massachusetts General Hospital, and all doses of OROS- MPH and placebo were delivered in identically appearing tablets" (Biederman 2010). 3. Stated, not tested.
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Dropout rates: methylphenidate 26 of 112 (23 %), placebo 17 of 115 (15 %). 2. Dropouts due to adverse events: methylphenidate 12 of 26, placebo 3 of 17. 3. Statistical method to account for missing data: mixed effects model repeated measures (Biederman 2010), general estimating equations with last observation carried forward (Biederman 2006).
Selective reporting (reporting bias)	High risk	1. Adverse event reporting threshold: No explicit threshold, only events reported at two or more visits were tabulated. 2. Several adverse events seemed to be categories rather than actual events, e.g. "cardiovascular", "neurological" and "musculosceletal" (See Biederman 2010, table 1). 3. Cardiovascular parametres and weight only reported in interim paper and not full study. 4. The Q-LES-QSF outcome was not reported.
Other bias	Low risk	None found.
Psychiatric comorbidity (External validity)	High risk	1. "Any clinically unstable psychiatric conditions including the following: acute psychosis, acute panic, acute OCD, acute mania, acute suicidality, bipolar disorder, acute substance use disorders (alcohol or drugs, sociopathy, criminality, or delinquency" (CT.gov).

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Biederman 2003 *(Continued)*

		2. "[Exclusion criteria] Other clinically unstable psychiatric conditions (ie, bipolar disorder, psychosis, suicidality), drug or alcohol abuse or dependence within the 6 months preceding the study" (Biederman 2010).
Responder selection (External validity)	Unclear risk	1. "Subjects with current adequate treatment for ADHD or a history of a previous adequate trial of Concerta" (were excluded). 2. It is unclear whether this means the participants were stimulant naïve.
Withdrawal effects (External validity)	Unclear risk	1. "[Exclusion criteria] Subjects with current adequate treatment for ADHD or a history of a previous adequate trial of Concerta" (CT.gov). 2. Current and previous stimulant use not described. 3. We were unsure how to interpret "adequate trial" and rated the domain as unclear.

Spencer 2003

Study characteristics	
Methods	**Trial ID(s)**: CRIT124E2302 (protocol), 2302 (FDA Review). **Trial registry entry**: Not registered. **Sponsor**: Novartis. **Funding/industry-involvement**: Industry trial **Setting:** USA. **No. sites**: 18. **Start - completion**: Apr 2003 - Sep 2003. **Duration**: 5 weeks. **Sample size**: 221.
Participants	*Information on exclusion criteria related to psychiatric comorbidity is listed in the risk of bias table.* **ADHD diagnostic system**: DSM IV. **Concomitant substance abuse diagnosis**: No. **Mean age (range)**: 39 (We noted the age range was 18-60, but they included participants up to 62 years of age). **Males** (%): 58.
Interventions	**Trial arms:** 1. Dex-methylphenidate extended-release 20 mg (n= 58) 2. Dex-methylphenidate extended-release 30 mg (n= 55) 3. Dex-methylphenidate extended-release 40 mg (n= 55) 4. Placebo (n= 53) **Type of methylphenidate**: dex-methylphenidate extended-release. **Dosage**: 20 mg to 40 mg. **Fixed or titrated**: Fixed. **Administrations per day**: 1.

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Spencer 2003 *(Continued)*

	Co-intervention(s): "Patients receiving any psychological or behavioral therapies for ADHD were also excluded" (FDA review p. 41)
Outcomes	*Relevant outcomes are listed here.* 1. CAARS Self: Short version (self-rated, 26 items, 0-78 points) 2. DSM IV Adult ADHD Rating Scale (investigator-rated, 18 items, 0-54 points) 3. Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (self-rated, 14 domains, 14-70 points) 4. Cardiovascular variables 5. Harms
Notes	**Declared conflicts of interest**: Conflicts of interests were not reported in (Spencer 2007) or the open-label extension (Adler 2009). The first and second authors declared the following interests in Adler 2006 trial: "**Dr Adler** receives grant/research support from the fol- lowing pharmaceutical companies: Abbott Laboratories, Cortex Pharmaceuticals, Bristol-Myers Squibb, Merck & Co, Novartis Pharmaceuticals, Pfizer, Eli Lilly, Shire, Ortho McNeil/Janssen/ Johnson and Johnson, New River Pharmaceuticals, Cephalon, and the National Institute of Drug Abuse. He is on the speaker's bureau for Eli Lilly and Shire. He serves on the advisory board and as a consultant for the following pharmaceutical com- panies: Abbott Laboratories, Cortex Pharmaceuticals, Novartis Pharmaceuticals, Pfizer, Eli Lilly, Shire, Ortho McNeil/Janssen/ Johnson and Johnson, New River Pharmaceuticals, Cephalon, Merck & Co, Organon, Sanofi-Aventis Pharmaceuticals, and Psychogenics. **Dr Spencer** receives research support from the following sources: Shire Laboratories Inc, Cephalon, Eli Lilly and Company, GlaxoSmithKline, Janssen, McNeil Pharmaceutical, Pfizer, Novartis Pharmaceuticals, and the National Institute of Mental Health. He is a speaker for the following speaker's bureaus: Shire Laboratories Inc, Eli Lilly and Company, GlaxoSmithKline, Janssen, McNeil Pharmaceutical, and Novar- tis Pharmaceuticals. He is on the advisory boards of the following pharmaceutical companies: Shire Laboratories Inc, Cephalon, Eli Lilly and Company, GlaxoSmithKline, McNeil Pharmaceutical, Pfizer, Janssen, and Novartis Pharmaceutical" (Adler 2006).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	1. "Subjects were equally randomised to each of the four treatment arm" (Spencer 2007).
Allocation concealment (selection bias)	Unclear risk	1. Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	1. "Matching placebo control. All capsules of study drug were identical in appearance" (CSR Synopsis). 2. Stated, not tested.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	1. "Matching placebo control. All capsules of study drug were identical in appearance" (CSR Synopsis). 2. Stated, not tested.
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Dropout rates: methylphenidate 27 of 168 (16 %), placebo 10 of 53 19 %. 2. Three participants were excluded after randomisation. 3. Dropouts due to adverse events: methylphenidate 18 (10,7 %), placebo 4 participants (7,5%). 4. Statistical method to account for missing data: Last observtion carried foward on ITT population for primary and secondary outcomes (Spencer 2007, p. 1382)

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Spencer 2003 *(Continued)*

Selective reporting (reporting bias)	High risk	1. Adverse event reporting threholds: Published report (five most frequent adverse events, 12,1 %), FDA Medical Review (0.6 % for Focalin XL), CSR Synopsis (14 adverse events reported, no stated threshold), FDA Prescriber Information (dose-dependent events, 5%). 2. "Severe adverse events", only those occuring in two or more participants were reported (Spencer 2007, p. 1384). 3. 'Dropouts due to adverse events' reported for events experienced by two or more participants (FDA Labelling, p. 12)
Other bias	Unclear risk	1. The FDA audit of trial sites discovered a case of miscoded reasons for withdrawal. The participant experienced multiple psychiatric adverse events before dropping out, but was coded as "withdrew consent" (FDA Admin and Correspondence, p. 14 of 41). 2. The FDA concluded (p. 16 of 41), "no underreporting of adverse events was noted". We judge the extent of miscoding and possible impact on the overall results is unclear.
Psychiatric comorbidity (External validity)	High risk	1. "Patients with a history of alcohol or substance abuse within the last 6 months were excluded, as were patients with any psychiatric or medical comorbidity that may have interfered with study participation or assessments or for which MPH treatment may have posed a risk" (Spencer 2007). 2. "Patients receiving any psychological or behavioral therapies for ADHD were also excluded" (FDA review p. 41).
Responder selection (External validity)	High risk	1. "Patients were also excluded if the investigator judged that they had a history of poor response or intolerance to stimulants (e.g., MPH, d-MPH, amphetamine salts, or dextroamphetamine salts)" (Spencer 2007). 2. Previous exposure to ADHD medication: methylphenidate 54 of 168 (32%) and placebo 26 of 53 (49%) (CSR Synopsis, p. 3) 3. Previous exposure to stimulants: methylphenidate arm 46 of 164 (28%), placebo 15 of 55 (27%) (Spencer 2007, table 1).
Withdrawal effects (External validity)	High risk	1. "Patients were also excluded if the investigator judged that they had a history of poor response or intolerance to stimulants (e.g., MPH, d-MPH, amphetamine salts, or dextroamphetamine salts)" (Spencer 2007). 2. Previous exposure to ADHD medication: methylphenidate 54 of 168 (32%) and placebo 26 of 53 (49%) (CSR Synopsis, p. 3) and exposure to stimulants: methylphenidate 46 of 164 (28%) and placebo 15 of 55 (27%) (Spencer 2007, table 1). 3. "Patients were required to discontinue all psychotropic drugs within 1 to 4 weeks prior to the screening visit" (Spencer 2007). 4. It was not described how many participants who were in current treatment and had to stop treatment before randomisation.

Chronis-Tuscano 2004

Study characteristics	
Methods	**Trial ID(s)**: NCT00318981, IIS-2003-023 (protocol). **Trial registry entry**: https://clinicaltrials.gov/ct2/show/NCT00318981. **Sponsor**: University of Maryland (ClinicalTrials.gov) **Funding/industry involvement**: McNeil listed as sponsor in article and as a collaborator on ClinicalTrials.gov. **Setting:** United States

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Chronis-Tuscano 2004 *(Continued)*

	No. sites: 1. **Start - completion**: Dec 2004 - Dec 2006 **Duration**: 2 weeks. **Sample size**: 20 participants.
Participants	*Information on exclusion criteria related to psychiatric comorbidity is listed in the risk of bias table.* **ADHD diagnostic system**: DSM IV. **Concomitant substance abuse disorder**: No. **Mean age (range)**: 40 (range not reported). **Males** (%): 0.
Interventions	**Trial arms:** 1. OROS methylphenidate (n= 9) 2. Placebo (n=11) **Type of methylphenidate**: OROS methylphenidate. **Dosage**: 36 mg to 90 mg. **Fixed or titrated**: Titrated. **Administrations per day**: Not described. **Co-intervention(s)**: "Psychosocial interventions should be suspended during the study".
Outcomes	*Relevant outcomes are listed here.* There were no results reported from the double-blind phase
Notes	**Declared conflicts of interest**: "Dr. Chronis-Tuscano has received grant/ research support from the National Institute of Mental Health (NIMH) (R34 MH073567-01A1). Dr. Stein has been a consultant for Novartis; has received grant/research support from Novartis, Pfizer, NIMH, and Eli Lilly; and has been a member of the speakers or advisory boards for McNeil and Novartis. Dr. Conlon has been a member of the speakers or advisory boards for McNeil Pediatrics, Eli Lilly, Novartis, and Shire. Dr. Robb has been a consultant for Lundbeck, Otsuka, and Eli Lilly; has received grant/research support from Pfizer, Janssen, Forest, Bristol-Myers Squibb, GlaxoSmithKline, Supernus, and NIMH; has received honoraria from the American Academy of Child and Adolescent Psychiatry; and has been a member of the speakers or advisory boards for McNeil Pediatrics, Eli Lilly, Abbott, and Bristol-Myers Squibb. Drs. Jones, Jiles, and Efron and Mss. Seymour, Rooney, Wagner, and Pian report no financial affiliations or other relationships relevant to the subject of this article" (Chronis-Tuscano 2008).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	1. "During Phase 2, mothers were randomly assigned to placebo or their maximally effective dose" (Chronis-Tuscano 2008).
Allocation concealment (selection bias)	Unclear risk	1. "During Phase 2, mothers were randomly assigned to placebo or their maximally effective dose" (Chronis Tuscano 2008).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	1. "Study physicians, research staff, and participants were blind to medication dose throughout the study". 2. The authors noted: "Also, it is often difficult to maintain participant blind in discontinuation studies such as this, given that participants who have previ-

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Chronis-Tuscano 2004 *(Continued)*

		ously experienced drug effects are more likely to be aware if they are being actively medicated or not (Chronis-Tuscano p. 1946). 3. Stated, not tested.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	1. "Study physicians, research staff, and participants were blind to medication dose throughout the study". 2. The authors noted: "Also, it is often difficult to maintain participant blind in discontinuation studies such as this, given that participants who have previously experienced drug effects are more likely to be aware if they are being actively medicated or not (Chronis-Tuscano p. 1946). 3. Stated, not tested.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1. No dropouts.
Selective reporting (reporting bias)	High risk	1. Adverse events, serious adverse events, blood pressure, pulse, and weight were not reported for the randomised phase (phase 2).
Other bias	Low risk	None found.
Psychiatric comorbidity (External validity)	High risk	1. "Mothers were excluded on the basis of any current Axis I disorder other than ADHD, Beck Depression Inventory-II scores consistently above 16 (N = 5), severe tics or Tourette's syndrome". 2. The authors noted "As such, our exclusion of participants with current comorbid disorders may limit the generalizability of these findings to real-world clinical settings" (Chronis-Tuscano p. 1946).
Responder selection (External validity)	High risk	1. The 2-week placebo-controlled phase was preceded with a 5-week titration phase for all participants meaning that all participants were exposed to methylphenidate before randomisation. 2. Previous exposure to stimulants not described.
Withdrawal effects (External validity)	High risk	1. The trial consisted of 2 phases. In phase 1, all participants were titrated to highest tolerated methylpehnidate dose afterwards they were randomised to placebo or continued methylphenidate. Washout between phase I and 2 was not described. 2. The authors noted: "It was expected that those randomly assigned to placebo would experience worsening of symptoms and parenting behavior from week 5 to 7, while those randomly assigned to their maximally effective dose would not evidence change" (Chronis-Tuscano p. 1944).

Rösler 2004

Study characteristics	
Methods	**Trial ID(s)**: NCT00619840, 6520-9979-06 (protocol), EMMA (trial name). **Trial registry entry**: https://clinicaltrials.gov/ct2/show/NCT00619840. **Sponsor**: Medice. **Country**: Germany. **No. sites**: 28. **Start - completion**: Nov 2004 - May 2006. **Duration**: 24 weeks.

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Rösler 2004 *(Continued)*

	Sample size: 359 participants.
Participants	*Information on exclusion criteria related to psychiatric comorbidity is listed in the risk of bias table.* **ADHD diagnostic system**: DSM IV. **Concomitant substance abuse disorder**: No. **Mean age (range)**: 35 years (18+) **Males** (%): 50.
Interventions	**Trial arms**: 1. Extended-release methylphenidate (n= 241) 2. Placebo (n= 118) **Type of methylphenidate**: Extended-release methylphenidate **Dosage range**: 10 mg ot 60 mg. **Fixed or titrated**: Titrated. **Administrations per day**: 2. **Co-intervention(s)**: Disease management sessions (7 sessions).
Outcomes	*Relevant outcomes are listed here.* 1. CAARS: Self DSM-IV total ADHD (Self-rated, items 18, 0-54 points) 2. Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS) (investigator, rated, 28 items, 0-56 points) 3. Cardiovascular variables 4. Harms
Notes	**Conflicts of interest**: Not reported in the primary publication. In Rösler 2010 they reported: "M. Rösler is speaker and member of the advisory board from Lilly Germany, Janssen-Cilag, Shire and Medice. He has received research support from Medice. He has grants from the German Federal Ministery of Education and Research. W. Retz has no financial interests in the connection with this manuscript. R. Fischer is the Medical Director of the study sponsor. C. Ose has received honoraria from Medice. B. Alm has no financial interests in connection with this study. J. Deckert has received honoraria from Medice and Janssen-Cilag. A. Philipsen is member of the advisory board of Medice and Janssen-Cilag. She has received research support from Medice. S. Herpertz has no financial interests in connection with this study. R. Ammer is member of the general management of the study sponsor Medice".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	1. "The participants (mean number 13 participants/study centre) were randomized to MPH ER or placebo at a ratio of 2:1" (Rösler 2009).
Allocation concealment (selection bias)	Unclear risk	1. "The participants (mean number 13 participants/study centre) were randomized to MPH ER or placebo at a ratio of 2:1" (Rösler 2009).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	1. "placebo-controlled". 2. Stated, not tested.
Blinding of outcome assessment (detection bias)	Unclear risk	1. "placebo-controlled". 2. Stated, not tested.

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Rösler 2004 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	High risk	1. Dropout rates: methylphenidate 58 of 241 (24 %), placebo 52 of 118 (43 %). 2. Dropouts due to adverse events methylphenidate 31 of 52, placebo 10 of 52. 3. Statistical method used to account for missing data: Last observation carried forward. 4. "Another field of limitations is the large drop-out rate in combination with the use of LOCF as imputation method", and "This may lead to concerns regarding the robustness of the conclusions drawn from the data" (Rösler 2009).
Selective reporting (reporting bias)	High risk	1. Adverse event reporting threshold: Published report (4 %, no threshold stated but for events occuring more frequently in the methylphenidate group this was the lower bar). 2. The adverse events list does not contain the "neurological abnormalities" mentioned in the text. 3. Serious adverse events not reported.
Other bias	Low risk	None found.
Psychiatric comorbidity (External validity)	High risk	1. "Individuals with low intelligence (IQ < 85), schizophrenia, bipolar disorder, acute depressive episode, acute anxiety disorders and other unstable psychiatric conditions were excluded, as were subjects with any serious medical illness" (Rösler 2009). 2. "Alcohol, medication or drug dependency in the past 6 months or manifest drug abuse" (CT.gov).
Responder selection (External validity)	High risk	1. "The proportion of individuals who had received earlier stimulant treatment was equal (38.2 vs. 38.3%) in both groups" (Rösler 2009) 2. "[exclusion criteria] Treatment with psychostimulants in the past 2 weeks" (CT.gov).
Withdrawal effects (External validity)	High risk	1. "[exclusion if] Treatment with psychostimulants in the past 2 weeks" (CT.gov). 2. "Individuals treated with any psychopharmacological drug in addition to study medication were not included. A wash- out period of at least 2 weeks was necessary for any psychopharmacological drug before study inclusion" (Rösler 2009). 3. "The proportion of individuals who had received earlier stimulant treatment was equal (38.2 vs. 38.3%) in both groups" (Rösler 2009)

Combine Substudy 2005

Study characteristics	
Methods	**Trial ID(s)**: NCT00261872, 06-AA-0004 (protocol) **Trial registry entry**: https://clinicaltrials.gov/ct2/show/NCT00261872 **Sponsor**: National Institute on Alcohol Abuse and Alcoholism (NIAAA). **Funding/industry involvement**: Not reported **Setting:** No data **No. sites**: No data **Start - completion**: Dec 2005 - Apr 2007 (est) **Duration**: 12 weeks.

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Combine Substudy 2005 *(Continued)*

	Sample size: No data.
Participants	*Information on exclusion criteria related to psychiatric comorbidity is listed in the risk of bias table.* **ADHD diagnostic system**: DSM IV **Concomitant substance abuse disorder**: DSM IV: Alcohol dependency **Mean age (range)**: No data (Range: 21 - 65) **Males** (%): No data
Interventions	**Trial arms:** 1. Slow released methylphenidate 2. Placebo **Type of methylphenidate**: "Slow released" methylphenidate **Dosage**: Not described. **Fixed or titrated**: Not described. **Administrations per day**: Not described. **Co-intervention(s):** Naltrexone + behavioural therapy
Outcomes	*Relevant outcomes are listed here.* We have no data from this study
Notes	**Declared conflicts of interest**: Conflicts not declared in the publication reporting on the main Combine study (Anton 2006)

Winhusen 2005

Study characteristics	
Methods	**Trial ID(s)**: NCT00253747, NIDA CTN-0029 (protocol), 5U10DA013732 (NIDA grant). **Trial registry entry**: https://clinicaltrials.gov/ct2/show/NCT00253747. **Sponsor**: University of Cincinnati **Funding/industry involvement**: NIDA grants (5U10DA013732), Janssen is listed as collaborator on ClinicalTrials.gov. **Country**: United States. **No. sites**: 6. **Start - completion**: Nov 2005 - Mar 2008. **Duration**: 11 weeks. **Sample size**: 255 participants
Participants	*Information on exclusion criteria related to psychiatric comorbidity is listed in the risk of bias table.* **ADHD diagnostic system**: DSM IV. **Concomitant substance abuse diagnosis**: No. **Mean age (range)**: 38 (years 18-55) **Males** (%): 57 %.

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Winhusen 2005 *(Continued)*

Interventions	**Trial arms**: 1. OROS methylphenidate (n= 127) 2. Placebo (n= 128) **Type of methylphenidate**: OROS methylphenidate. **Dosage range**: 18 mg to 72mg. **Fixed or titrated**: Titrated. **Administrations per day**: 1. **Co-intervention(s)**: Nicotine patch + smoking cessation counseling (weekly).
Outcomes	*Relevant outcomes are listed here.* 1. ADHD DSV IV total score (investigator-rated, 18 items, range 0 to 54) 2. Cardiovascular variables 3. Harms
Notes	**Declared conflicts of interest**: "Dr Adler is a consultant for Abbott Laboratories, Cortex Pharmaceuticals, Novartis Pharmaceuticals, Pfizer, Shire, Eli Lilly, Ortho McNeil/Janssen/Johnson and Johnson, New River Pharmaceuticals, Cephalon, Merck, Organon, Sanofi-Aventis Pharmaceuticals, Psychogenics, Mindsite, Major League Baseball, and Psychogenics; has received grant/research support from Abbott Laboratories, Cortex Pharmaceuticals, Bristol-Myers Squibb, Merck and Co, Novartis Pharmaceuticals, Pfizer, Shire, Eli Lilly, Ortho McNeil/ Janssen/Johnson and Johnson, New River Pharmaceuticals, Cephalon, and the National Institute of Drug Abuse; is a member of the speakers/advisory boards for Abbott Laboratories, Cortex Pharmaceuticals, Novartis Pharmaceuticals, Pfizer, Shire, Eli Lilly, Ortho McNeil/Janssen/Johnson and Johnson, New River Pharmaceuticals, Cephalon, Merck, Organon, Sanofi-Aventis Pharmaceuticals, Eli Lilly, and Shire; and has received royalty payments (as inventor) from NYU for license of adult ADHD scales and training materials. Dr Weiss is a consultant for Titan Pharmaceuticals and has received grant/research support from Eli Lilly. Drs Winhusen, Somoza, Brigham, Liu, Green, Covey, Croghan, and Leimberger and Mr Lewis and Ms Dorer have no personal affiliations or financial relationships with any commercial interest to disclose relative to the article" (Winhusen 2010)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	1. "Randomization of participants to OROS-MPH or matching placebo was in a 1:1 ratio, stratified by site, and completed by computer at a centralized location" (Winhusen 2010).
Allocation concealment (selection bias)	Low risk	1. "Randomization of participants to OROS-MPH or matching placebo was in a 1:1 ratio, stratified by site, and completed by computer at a centralized location" (Winhusen 2010).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	1. "matching placebo". 2. Stated, not tested.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	1. "matching placebo". 2. Stated, not tested.

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Winhusen 2005 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	1. Dropout rates: methylphenidate (24/127) 19 %, placebo (27/128), 21 %. 2. Dropout due to adverse events: methylphenidate (0/24) and placebo (0/27) 3. Statistical method used to account or missing data: General Estimation Equation (GEE) model for ADHD symptom rating. Assumes that missing data is random. 4. Extra observation: Low number of completers for the investigator rated ADHD symptoms: 38 for methylphenidate and 42 for placebo.
Selective reporting (reporting bias)	High risk	1. Adverse event reporting thresholds: Published report (5%), ct.gov (3%).
Other bias	Low risk	None found.
Psychiatric comorbidity (External validity)	High risk	1. "Candidates were excluded if they were a significant suicidal/homicidal risk; had used tobacco products other than cigarettes in the past week; had a positive urine screen for an illicit drug; or met DSM-IV criteria for current abuse or dependence for any psychoactive substance other than nicotine, current major depression, any current anxiety disorder except specific phobias, antisocial personality disorder, or a lifetime diagnosis of bipolar disorder or psychosis" (Winhusen 2010).
Responder selection (External validity)	High risk	1. "Individuals were also excluded if they had been treated for ADHD with psychomotor stimulants […] within the last 30 days" (Winhusen) 2. "If they had a known allergy to OROS-MPH, or if they had been non-responders to a reasonable course of MPH treatment" (Winhusen 2010).
Withdrawal effects (External validity)	High risk	1. "Individuals were also excluded if they had been treated for ADHD with psychomotor stimulants or had used smoking cessation counseling programs or medications within the last 30 days" (Winhusen 2010).

Medori 2005

Study characteristics	
Methods	**Trial ID(s)**: NCT00246220, 2004-000730-37 (EUCTR), CR002479 (protocol), 42603ATT3002 (FDA review), Study 4 (Aus PI), and Study 5 (Health Canada Drug Monograph), LAMDA (trial name). **Trial registry entry**: https://clinicaltrials.gov/ct2/show/NCT00246220, https://www.clinicaltrialsregister.eu/ctr-search/trial/2004-000730-37/DK. **Sponsor**: Janssen. **Setting**: 13 European countries. **No. sites**: 48 sites. **Start - completion**: Apr 2005 - Aug 2006. **Duration**: 5 weeks. **Sample size**: 402 participants.
Participants	*Information on exclusion criteria related to psychiatric comorbidity is listed in the risk of bias table.* **ADHD diagnostic system**: DSM IV. **Concomitant substance abuse disorder**: No. **Mean age (range)**: 34 years (18-63) **Males** (%): 54

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Medori 2005 *(Continued)*

Interventions	**Trial arms:** 1. OROS methylphenidate 18 mg (n= 101) 2. OROS methylphenidate 36 mg (n= 102) 3. OROS methyphenidate 72 mg (n= 103) 4. Placebo (n= 96) **Type of methylphenidate**: OROS methylphenidate. **Dosage**: 18 mg to 72 mg. **Fixed or titrated**: Fixed. **Administrations per day**: 1 **Co-intervention(s)**: Not described.
Outcomes	*Relevant outcomes are listed here.* 1. CAARS - SHORT (Self-rated, 26 Items, 0-78 points) 2. CAARS: Observer - DSV IV Total Symptoms (Investigator-rated, 18 items, 0-54 points) 3. Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-QSF) (Self-rated, 14 items, 14-70 points) 4. Cardiovascular variables 5. Harms
Notes	**Declared conflicts of interest**: "We thank the investigators, their study teams, and patients for participating in the study. Joachim Dejonckheere of SGS Life Sciences analyzed the data. We also acknowledge Bradford Challis, Ph.D., and Susan Glasser, Ph.D., of Johnson & Johnson Pharmaceutical Research & Development, L.L.C., for their con- tribution to the preparation of the manuscript.Drs. Rossella Medori and Emma Lee are employees of Janssen, and the other authors were investigators in the clinical study. Dr. Ramos-Quiroga reports having received lecture and consulting fees from Janssen-Cilag and Laboratorios Rubio´and research funding from Janssen-Cilag. Dr. Casas reports having received lecture and consulting fees from Janssen-Cilag and Laboratorios Rubio´and research funding from Janssen-Cilag. Dr. Kooij reports having been a consultant, member of advisory board, and/or speaker for Janssen Cilag BV and Eli Lilly. Dr. Buitelaar reports having been a consultant, member of advisory board, and/or speaker for Janssen Cilag BV, Eli Lilly, Bristol-Myer Squibb, UBC, Shire, Medice. Dr. Niemelä reports having received lecture fees from Janssen-Cilagand. Dr. Trott reports no applicable financial interests or potential conflicts of interest" (Medori 2008).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	1. "Randomization was based on a computer-generated randomization and stratification scheme prepared before the study. Randomization was balanced by using permuted blocks of treatments, stratified by study center, and implemented via an interactive voice response system" (Medori 2008).
Allocation concealment (selection bias)	Low risk	1. "Randomization was based on a computer-generated randomization and stratification scheme prepared before the study. Randomization was balanced by using permuted blocks of treatments, stratified by study center, and implemented via an interactive voice response system" (Medori 2008).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	1. "placebo-controlled" (Medori 2008). 2. Stated, not tested.

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Medori 2005 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	1. "placebo-controlled" (Medori 2008). 2. Stated, not tested.
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Dropout rates: methylphenidate 31 of 306 (10 %) and placebo 6 of 96 (6 %). 2. Dropouts due to adverse events: methylphenidate 12 of 31 and placebo 0 of 6. (Supplementary 2). 3. Statistical method to account for missing data: Last observation carried forward and actual values for the secondary outcomes (Medori 2008).
Selective reporting (reporting bias)	Unclear risk	1. Adverse event reporting threshold: CSR Synopsis (5 %), published report (3%), FDA Medical Review and Health Canada Drug Monograph (2%), Australian Prescribing Information (1%, combined Medori, Adler, Casas). 2. There were discepancies between the adverse event reporting in the MHRA Public Assessment Report between tables on page 60 and 62 for the outcomes of depression and aggression. 3. We do not know the actual adverse event reporting threshold for the trial in the pooled reporting in the Australian Prescribing Information, therefore we rated as unclear.
Other bias	Low risk	None found.
Psychiatric comorbidity (External validity)	High risk	1. "Any clinically unstable psychiatric condition including, but not limited to the following: acute mood disorder, bipolar disorder, acute obsessivecompulsive disorder (OCD), antisocial personality disorder, borderline personality disorder. Subjects with a family history of schizophrenia or family history of affective psychosis. Autism or Asperger's syndrome. Subjects with presence of motor tics, history of Tourette's syndrome or family history of Tourette's syndrome. A diagnosis of substance use disorder (abuse/dependence) according to DSMIV criteria within 6 months prior to screening evaluation (nicotine and caffeine dependence are not exclusionary). Episodic abuse in the past is not an exclusion criterion. Current eating disorder (e.g. bulimia, anorexia nervosa) or history of an eating disorder" (EUCTR).
Responder selection (External validity)	High risk	1. "Known to be a nonresponder to methylphenidate, or subject has a child known to be a nonresponder to methylphenidate" (EUCTR) 2. "Has been treated with any methylphenidatecontaining medication within 1 month of screening visit. One month is considered a reasonable time for patients treated with methylphenidate to return to a disease status baseline" (EUCTR). 3. "Known allergy or hypersensitivity to methylphenidate, or components of PR OROS methylphenidate" (EUCTR). 4. "The majority of subjects were stimulant naïve with 13% having been on prior stimulants" (FDA Medical Review, p. 87 of 456).
Withdrawal effects (External validity)	High risk	1. "[exclusion criteria] Has been treated with any methylphenidatecontaining medication within 1 month of screening visit. One month is considered a reasonable time for patients treated with methylphenidate to return to a disease status baseline" (EUCTR). 2. "The majority of subjects were stimulant naïve with 13% having been on prior stimulants" (FDA Medical Review, p. 87 of 456).

Konstenius 2006

Study characteristics

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Konstenius 2006 *(Continued)*

Methods	**Trial ID(s)**: ISRCTN81602628. **Trial registry entry**: http://www.isrctn.com/ISRCTN81602628. **Sponsor**: Addiction Centre Stockholm, Sweden. **Funding/industry involvement**: None. **Country**: Sweden. **No. trial sites**: 1. **Start - completion**: Feb 2006 - Jun 2007. **Duration**: 12 weeks. **Sample size**: 24
Participants	*Information on exclusion criteria related to psychiatric comorbidity is listed in the risk of bias table.* **ADHD diagnostic system**: DSM IV **Concomitant substance abuse diagnosis**: DSM IV: Amphetamine dependence **Mean age (range)**: 37 years (18-65) **Males** (%): 79.
Interventions	**Trial arms**: 1. OROS methylphenidate (n= 12) 2. Placebo (n= 12) **Type of methylphenidate**: OROS methylphenidate. **Dosage**: 18 mg to 72 mg. **Fixed or titrated**: Titrated. **Administrations per day**: 1. **Co-intervention(s)**: Skills training program (weekly).
Outcomes	*Relevant outcomes are listed here.* 1. CAARS: self rating (Self-rated, unspecified) 2. CAARS: Observer Rating (Investigator-rated unspecified)
Notes	**Conflicts of interest**: "There are no conflicts of interest to declare" (Konstenius 2010).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	1. "Twenty-four participants were randomized to either PL or MPH by the Karolinska University Hospital Pharmacy, using the Trombul software" (Konstenius 2010).
Allocation concealment (selection bias)	Low risk	1. "Twenty-four participants were randomized to either PL or MPH by the Karolinska University Hospital Pharmacy, using the Trombul software" (Konstenius 2010).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	1. "This study was a double-blind, placebo controlled, randomized trial" (Konstenius 2010). 2. Stated, not tested.

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Konstenius 2006 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	1. "This study was a double-blind, placebo controlled, randomized trial" (Konstenius 2010). 2. Stated, not tested.
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Dropout rates: methylphenidate 5 of 12 (42 %), placebo 2 of 12 (17 %). 2. Dropouts due to adverse events: not reported. 3. Statistical method used to account for missing data: Last observation carried forward (as reported in table 1, although in the method's section it says they used completer's population).
Selective reporting (reporting bias)	High risk	1. Adverse event reporting threshold: No specific threshold, but non systematic reporting of type and frequency. 2. SAEs not reported. It seems that no SAEs occured, but it is not directly reported.
Other bias	Low risk	None found.
Psychiatric comorbidity (External validity)	High risk	1. "Exclusion criteria included: (1) current or past DSM IV diagnosis of any other substance dependence except nicotine, (2) history of any major psychiatric disorder (e.g., schizophrenia and major depression) or any current psychiatric condition requiring medication" (Konstenius 2010).
Responder selection (External validity)	High risk	1. "Known hypersensitivity for methylphenidate" (Konstenius 2010). 2. "[Inclusion criteria] Amphetemine (amph) dependence according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)" (ISRCTN).
Withdrawal effects (External validity)	High risk	1. "Amphetemine (amph) dependence according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)" (ISRCTN). 2. "Participants are required to stay abstinent of any substance for minimum two weeks prior the inclusion" (ISRCTN).

Adler 2006

Study characteristics	
Methods	**Trial ID(s)**: NCT00326391, CR011560 (protocol), 02-159 (FDA, MHRA), Study 5 (Aus PI). **Trial registry entry**: https://clinicaltrials.gov/ct2/show/NCT00326391. **Sponsor**: McNeil (CT.gov), Johnson & Johnson (CSR synopsis, publication). **Funding/industry-involvement**: Industry trial. **Location**: United States. **No. sites**: 27 sites. **Start - completion**: April 2006 - Dec 2006. **Duration**: 7 weeks. **Sample size**: 229 participants.
Participants	*Information on exclusion criteria related to psychiatric comorbidity is listed in the risk of bias table.* **ADHD diagnostic system**: DSM IV. **Concomitant substance abuse diagnosis**: No. **Mean age (range)**: 39 years (18-65).

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Adler 2006 *(Continued)*

	Males (%): 56.
Interventions	**Trial arms**: 1. OROS methylphenidate (n= 113) 2. Placebo (n= 116) **Type of methylphenidate**: Osmotic-controlled release oral delivery system (OROS) methylphenidate. **Dosage range**: 36 mg to 108 mg. **Fixed or titrated**: Titrated **Administrations per day**: 1. **Co-intervention(s)**: Not described.
Outcomes	*Relevant outcomes are listed here.* 1. CAARS: Self short version (self-rated, 26 items, 0-78 points) 2. Adult ADHD Investigator Symptom Report Scale (AISRS) (investigator-rated, 18 items, 0 - 54 points) 3. Cardiovascular variables 4. Harms
Notes	**Declared conflicts of interest**: "Dr Adler receives grant/research support from the fol- lowing pharmaceutical companies: Abbott Laboratories, Cortex Pharmaceuticals, Bristol-Myers Squibb, Merck & Co, Novartis Pharmaceuticals, Pfizer, Eli Lilly, Shire, Ortho McNeil/Janssen/ Johnson and Johnson, New River Pharmaceuticals, Cephalon, and the National Institute of Drug Abuse. He is on the speaker's bureau for Eli Lilly and Shire. He serves on the advisory board and as a consultant for the following pharmaceutical com- panies: Abbott Laboratories, Cortex Pharmaceuticals, Novartis Pharmaceuticals, Pfizer, Eli Lilly, Shire, Ortho McNeil/Janssen/ Johnson and Johnson, New River Pharmaceuticals, Cephalon, Merck & Co, Organon, Sanofi-Aventis Pharmaceuticals, and Psychogenics. Dr Spencer receives research support from the following sources: Shire Laboratories Inc, Cephalon, Eli Lilly and Company, GlaxoSmithKline, Janssen, McNeil Pharmaceutical, Pfizer, Novartis Pharmaceuticals, and the National Institute of Mental Health. He is a speaker for the following speaker's bureaus: Shire Laboratories Inc, Eli Lilly and Company, GlaxoSmithKline, Janssen, McNeil Pharmaceutical, and Novar- tis Pharmaceuticals. He is on the advisory boards of the following pharmaceutical companies: Shire Laboratories Inc, Cephalon, Eli Lilly and Company, GlaxoSmithKline, McNeil Pharmaceutical, Pfizer, Janssen, and Novartis Pharmaceutical. Drs Starr, Silber, Palumbo, and Orman, and Ms Zimmerman, are all employees of Johnson and Johnson. Dr Starr also owns stock in Johnson and Johnson" (Adler 2009).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	1. "Subjects were randomized using a computer-generated randomization schedule stratified by investigator site with a block size of 4" (Adler 2009)
Allocation concealment (selection bias)	Low risk	1. "To randomize subjects, a qualified study staff used an interactive voice recognition system and entered the subject's date of birth, sex, and responses to selected eligibility questions. The system first verified that each subject randomized was unique and then, following the randomization schedule, identified the unique kit number of the dosing package that the study staff was to dispense to the subject at the baseline visit" (Adler 2009).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	1. "Each investigator received an allotment of double-blind medication before the study started, and each subject received overencapsulated tablets that appeared identical to the treatment of all other subjects at the beginning of the study" (Adler 2009). 2. Stated, not tested.

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Adler 2006 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	1. "Each investigator received an allotment of double-blind medication before the study started, and each subject received overencapsulated tablets that appeared identical to the treatment of all other subjects at the beginning of the study" (Adler 2009). 2. Stated, not tested.
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Dropout rates: methylphenidate 42 of 113 (37 %), placebo 26 of 116 (22 %). 2. Dropouts due to adverse events: methylphenidate 16 of 42, placebo 6 of 26. 3. Statistical method used to acount for missing data: Last observation carried forward.
Selective reporting (reporting bias)	High risk	1. Adverse event reporting threshold: Published paper (5 %), CSR synopsis (no threshold but it only mentioned "the most commonly" adverse events), FDA Medical Review (1 %). 2. The outcomes Q-LES-Q-SF and AIM-A were mentioned in the FDA review and CSR synopses (from YODA and CT.gov) but not reported. One domain (work/home/school) was reported in the MHRA report, but not the AIM-A overall quality of life score like for Casas 2008. 3. There were discepancies between the adverse event reporting in the MHRA Public Assessment Report between tables on page 60 and 62 for the outcomes of depression and aggression.
Other bias	Low risk	None found.
Psychiatric comorbidity (External validity)	High risk	1. "Subjects with symptoms of marked anxiety, tension, agitation, or a HAM-A score of 21 or greater or with symptoms of moderate severity of depression ratings using a HAM-D score of 17 or higher were excluded" (Adler 2009). 2. "The patients who met the DSM- IV criteria for depressive or anxiety disorders were excluded from the study, even if their HAM scores did not reach these cutoffs" (Adler 2009). 3. "Patients with comorbid psychiatric diagnosis per DSM-IV criteria of bipolar disorder, cyclothymic disorder, schizophrenia, pervasive developmental disorder, severe obsessive-compulsive disorders, or any other diagnosis that in the judgment of the investigator could have deemed the subject to be inappropriate for the study were excluded" (Adler 2009). 4. "Subjects with a history of drug or alcohol abuse within the past 6 months" (Adler 2009). 5. "Subjects with moderated depression, marked anxiety, suicidal ideation, or drug or alcohol dependence were also excluded from the study. Therefore, these data may not generalize to adult patients who are not otherwise healthy" (Adler 2009, p. 246).
Responder selection (External validity)	High risk	1. "Known nonresponders to methylphenidate were also excluded, as were subjects with a history of allergy to methylphenidate" (Adler 2009). 2. "Most subjects (93.0%) were not taking ADHD medication at baseline; 35,4 % had previously taken medications for ADHD" (Adler 2009).
Withdrawal effects (External validity)	High risk	1. "Subjects being treated for ADHD at screening were washed out from all ADHD medication for 7 to 14 days before beginning the study" (Adler 2009). 2. "Most subjects (93.0%) were not taking ADHD medication at baseline; 35.4% had previously taken medications for ADHD" (Adler 2009). 3. Baseline measures were recorded after the 1-2 weeks of washout, including ADHD symptoms (FDA Review, p. 91 of 456).

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Compas 2007 CM

Study characteristics	
Methods	See description for COMPAS GPT
Participants	
Interventions	
Outcomes	
Notes	

Konstenius 2007

Study characteristics	
Methods	**Trial ID(s)**: 2006-002249-35, ISRCTN77940178, MKJF001. **Trial registry entry**: https://www.clinicaltrialsregister.eu/ctr-search/trial/2006-002249-35/SE. **Sponsor**: Addiction Centre Stockholm, National Psychiatric Services Coordination Taskgroup. **Funding/industry involvement**: None **Country**: Sweden. **No. trial sites**: 1. **Start - completion**: April 2007 - Sep 2011. **Duration**: 24 weeks. **Sample size**: 54
Participants	*Information on exclusion criteria related to psychiatric comorbidity is listed in the risk of bias table.* **ADHD diagnostic system**: DSM IV. **Concomitant substance abuse diagnosis**: DSM IV: Amphetamine dependence. **Mean age (range)**: 42 years (18-65). **Males** (%): 100. **Other trial characteristics**: Only criminal offenders were included. Treatment started two weeks before realease from prison and continued for 22 weeks after release.
Interventions	**Trial arms**: 1. OROS methylphenidate (n= 27) 2. Placebo (n= 27) **Type of methylphenidate**: OROS methylphenidate. **Dosage**: 18 mg to 180 mg. **Fixed or titrated**: Titrated. **Administrations per day**: 1. **Co-intervention(s)**: Cognitive behavioural therapy (first 12 weeks), meeting with psychologist/coach (week 13-24, every 14 days).
Outcomes	*Relevant outcomes are listed here.*

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Konstenius 2007 *(Continued)*

1. CAARS:DSM IV total ADHD (Self-rated, 18 items, 0-54 points)
2. Harms

Notes	**Declared conflicts of interest**: "The authors declare no conflicts of interest" (Konstenius 2013).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	1. "The randomization list was generated by an independent pharmacist using the computer-based program design by Trombult Programing. Between March 2007 and February 2011, 54 subject numbers were randomized into two parallel groups (MPH or identical placebo) with the block size 2" (Konstenius 2014).
Allocation concealment (selection bias)	Low risk	1. "The randomization code was retained by the Karolinska Pharmacy and disclosed after the end of the trial. No interim analysis was performed" (Konstenius 2014).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	1. "MPH or identical placebo" (Konstenius 2014). 2. "Block randomization was used because of the length of the trial and the nature of the medication effect, and was unknown to the principle investigator and the study staff" (Konstenius 2014). 3. "Although efforts were made to maintain blinding, 48% of the participants receiving MPH and 48% of the placebo group identified their medication correctly during the titration phase or after reaching the maximum dose. However, many of the participants in both treatment groups remained uncertain (41% MPH, 26% placebo) or were wrong (11% MPH, 26% placebo) about which treatment arm they were allocated to" (Konstenius 2014).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	1. "MPH or identical placebo" (Konstenius 2014). 2. "Block randomization was used because of the length of the trial and the nature of the medication effect, and was unknown to the principle investigator and the study staff" (Konstenius 2014). 3. Stated, not tested for investigators
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Dropout rates: methylphenidate 17 of 27 (63 %), placebo 23 of 27 (85 %). 2. Reasons for dropouts: not described for respectively (14/17) and (19/23) of the participants. They were labelled as "dropouts" only (Figure 1). 3. Statistical method to account for missing data: Last observation carried forward.
Selective reporting (reporting bias)	High risk	1. Serious adverse events not reported for the placebo group. 2. Blood pressure, pulse, and weight values not reported for the placebo group. 3. The "relapse to crime" outcome was not reported. 4. The CGI-Improvement and CGI-Severity were not reported.
Other bias	Low risk	None found.
Psychiatric comorbidity (External validity)	Low risk	1. "The study exclusion criteria were: (i) DSM-IV diagnosis of any other substance dependence except nicotine, currently or during the 12 months prior to incarceration, (ii) a major psychiatric disorder (e.g. schizophrenia, severe depression)" (Konstenius 2014).
Responder selection (External validity)	High risk	1. "Known hypersensitivity to methylphenidate" (ISRCTN) 2. "Those who meet the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV) criteria for amphetamine addiction" (ISRCTN).

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Konstenius 2007 *(Continued)*

Withdrawal effects (External validity)	High risk	1. "Those who meet the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV) criteria for amphetamine addiction" (ISRCTN). 2. "All participants met the diagnostic criteria for amphetamine dependence during the last 12 months prior to the current incarceration, and had used amphetamines on a minimum of 12 occasions during the last 12 weeks preceding the incarceration" (Konstenius 2014). 2. "All participants had i.v. amphetamine use" (#4078). 3. "Patients were required to abstain from any illicit substances during the 2 weeks preceding the inclusion" (Konstenius 2014).

Ginsberg 2007

Study characteristics	
Methods	**Trial ID(s)**: NCT00482313, 2006-002553-80 (EUCTR), ADHD Norrtälje 2006 (protocol), 6104/2009-305 F27&28 (Project ID). **Trial registry entry**: https://clinicaltrials.gov/ct2/show/NCT00482313. **Sponsor**: Karolinska University Hospital. **Funding/industry involvement**: None **Country**: Sweden. **No. sites**: 1. **Start - completion**: May 2007 - April 2010. **Duration**: 5 weeks. **Sample size**: 30 participants.
Participants	*Information on exclusion criteria related to psychiatric comorbidity is listed in the risk of bias table.* **ADHD diagnostic system**: DSM IV. **Concomitant substance abuse diagnosis**: No. **Mean age (range)**: 34 years (21-61) **Males** (%): 100.
Interventions	**Trial arms**: 1. OROS methylphenidate (n= 15) 2. Placebo (n= 15) **Type of methylphenidate**: OROS methylphenidate. **Dosage range**: 72 mg. **Fixed or titrated**: Fixed. **Administrations per day**: 1. **Co-intervention(s)**: Personal psychosocial treatment (not ADHD-specific, on a daily level).
Outcomes	*Relevant outcomes are listed here.* 1. Adult ADHD Self-Report Scale (ASRS) (Self-rated, 18 items, 0-72 points) 2. CAARS: Observer Rating (Investigator-rated, 18 items, 0-54 points) 3. Cardiovascular variables 4. Harms

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Ginsberg 2007 *(Continued)*

Notes	**Declared conflicts of interest**: Not reported in the primary publication (Ginsberg 2015). In the 3-year follow-up study they reported: "This was an investigator-initiated study funded by the Swedish Ministry of Health and Social Affairs and the Stockholm County Council, Sweden. Dr Ginsberg has served as an investigator, consultant and/or speaker for Novartis, Eli Lilly, HB Pharma, and Shire. Dr Larsson has served as a speaker for Eli Lilly and received a research grant from Shire. Dr Långström received one speaker's honorarium from Lundbeck in 2013, and Dr Lindefors has no conflicts to declare" (Ginsberg 2015).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	1. "The pharmacy laboratory assigned participants to the two study groups using a random number table prior to preparing and dispensing the study drug according to the study protocol" (Ginsberg 2012).
Allocation concealment (selection bias)	Low risk	1. "The random number table was stored in the pharmacy department and was concealed from study staff and participants until completion of the study" (Ginsberg 2012).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	1. "The placebo and methylphenidate capsules and packaging were identical in appearance and were coded with a unique randomisation number" (Ginsberg 2012). 2. "Both study staff and participants were masked to assignment during the RCT" (Ginsberg 2012). 3. Stated, not tested.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	1. "The placebo and methylphenidate capsules and packaging were identical in appearance and were coded with a unique randomisation number" (Ginsberg 2012). 2. "Both study staff and participants were masked to assignment during the RCT" (Ginsberg 2012). 3. "In most cases, the same specifically trained and masked assessor performed the evaluations [...]." (Ginsberg 2012). 4. Stated, not tested.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1. Dropout rates: methylphenidate 0 of 15 (0 %), placebo 0 of 15 (0 %). 2. Dropouts due to adverse events: none. 3. Statistical method to account for missing data: Last observation carried forward. It is not clear why they would use LOCF when there were no dropouts.
Selective reporting (reporting bias)	Low risk	1. Adverse event reporting threshold: Yearly report (in Swedish) (full reporting), published paper (non-systematic reporting). 2. The QOLI outcome was not measured during the double-blind phase and therefore does not count as selective outcome reporting.
Other bias	Low risk	None found.
Psychiatric comorbidity (External validity)	Unclear risk	1. "[exclusion criteria] Any clinically unstable psychiatric condition including, but not limited to, acute mood disorder, bipolar disorder, acute OCD. A diagnosis of substance use disorder (abuse/dependence) according to DSM-IV criteria within 3 months prior to screening evaluation for the study." (CT.gov). 2. "Participants with comorbid disorders such as autism-spectrum disorder, anxiety and depression could take part if they were considered to be stable at baseline. Previous drug- elicited episodes of psychosis were not a cause for exclusion, other than chronic psychoses" (Ginsberg 2012).

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Ginsberg 2007 *(Continued)*

		3. "In contrast to most previous treatment studies of adult ADHD, we did not exclude participants with current treatment for comorbid disorders, unless the concurrent treatment interfered with the activity of methylphenidate. This allowed us to extend the external validity of the results to a broader ADHD population" (Ginsberg 2012, p. 72). 4. We rate this domain as unclear since the exclusion criteria listed on Ct.gov/EUCTR seem strict whereas it is described in the article that they were less restrictive.
Responder selection (External validity)	High risk	1. "Participants were excluded if they were known to be non- responsive or intolerant to methylphenidate" (Ginsberg 2012). 2. "Five inmates had previously been treated with methylphenidate", corresponding to 17 % of population 3. "None of the inmates were known to be non-responsive or intolerant to methylphenidate" (Ginsberg 2012).
Withdrawal effects (External validity)	High risk	1. 18 of 30 participants had a primary amphetamine sustance abuse diagnosis (Ginsberg 2012, supplement). 2. "The screening visit took place up to 2 weeks before randomisation to enable medications excluded from the study to be tapered off prior to the baseline visit". 3. "Five inmates had previously been treated with methylphenidate" (Ginsberg 2012). 4. "Participants were excluded if they showed evidence of substance misuse up to 3 months before baseline, assessed in urine samples" (Ginsberg 2012)

Compas 2007 GPT

Study characteristics	
Methods	**Trial ID(s)**: 2006-000222-31 (EUCTR), ISRCTN54096201, 70170 (protocol). **Trial registry entry**: https://www.clinicaltrialsregister.eu/ctr-search/trial/2006-000222-31/DE, http://www.isrctn.com/ISRCTN54096201. **Sponsor**: Universitätsklinikum Freiburg **Funding/industry involvement**: German Federal Ministry of Education and Research (01GV0605 and 01GV0606). The Marketing Authorisation Holder, Medice, was involved in the study design and outcome collection **Country**: Germany. **No. sites**: 7 sites. **Start - completion**: April 2007 - Aug 2011. **Duration**: 52 weeks. **Sample size**: 433 participants.
Participants	*Information on exclusion criteria related to psychiatric comorbidity is listed in the risk of bias table.* **ADHD diagnostic system**: DSM IV. **Concomitant substance abuse diagnosis**: No. **Mean age (range)**: 35 years (18-58). **Males** (%): 53 (for group psychotherapy-comparison), 47 (for clinical management comparison).
Interventions	**Trial arms**:

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Compas 2007 GPT *(Continued)*

1. Extended-release methylphenidate + clinical management (n= 110)
2. Placebo + clinical management (n= 107)
3. Extended-release methylphenidate + group psychotherapy (n= 107)
4. Placebo + group psychotherapy (n= 109)

Type of methylphenidate: Extended-release methylphenidate.
Dosage range: 10 mg to 60 mg or up to 1.3 mg/kg.

Fixed or titrated: Titrated.

Administrations per day: 2.

Co-intervention(s): Group psychotherapy (weekly until w12, monthly afterwards) or clinical management, non-specific counseling in individual sessions (weekly until w12, afterwards monthly)

Outcomes

Relevant outcomes are listed here.

1. Absence from work/education/training
2. CAARS: DSM-IV total ADHD (Self-rated, 18 items, 0-54 points)
3. CAARS-O:L DSM-IV ADHD Symptoms Total (Investigator-rated, 18 items, 0–54 points).
4. Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-QSF) (Self-rated, 14 items, 14-70 points)
5. Harms

Notes

Declared conflicts of interest: "Dr Philipsen reported serving on advisory boards, giving lectures, performing phase 3 studies, or receiving travel grants within the last 3 years from Eli Lilly and Co, Janssen-Cilag, MEDICE Arzneimittel Pütter GmbH and Co KG, Novartis, and Shire; and has authored books and articles on psychotherapy published by Elsevier, Hogrefe, Schattauer, Kohlhammer, and Karger. Dr Matthies reported receiving a speaker's fee from Janssen-Cilag; and involvement in clinical trials conducted by Janssen- Cilag and Eli Lilly and Co. Dr Colla reported serving on advisory boards, receiving speaker's honoraria, or performing phase 3 studies within the last 3 years with Shire, Eli Lilly and Co, and Novartis. Dr Jacob reported receiving speaker's honoraria from MEDICE; serving as an advisory board member of Eli Lilly and Co; performing phase 3 studies at MEDICE, Novartis, Janssen-Cilag, Eli Lilly and Co; and performing an investigator-initiated trial with Eli Lilly and Co. Dr Sobanski reported receiving speaker's honoraria from MEDICE, Eli Lilly and Co, and Novartis; serving as an advisory board member of MEDICE, Shire, and Eli Lilly and Co; and performing phase 3 studies and investigator-initiated trials with MEDICE, Novartis, Janssen-Cilag, and Eli Lilly and Co. Dr Alm reported receiving speaker's honoraria from MEDICE; serving on the advisory board of Eli Lilly and Co; performing phase 3 studies at MEDICE, Novartis, Janssen-Cilag, Eli Lilly and Co; and performing an investigator-initiated trial with Eli Lilly and Co. Dr Roesler reported serving as an advisory board member of MEDICE, Eli Lilly and Co, and Janssen-Cilag; serving as a member of the speakers bureau of MEDICE, Eli Lilly and Co, Shire, and Novartis; and performing clinical studies for MEDICE. Dr Retz reported receiving speaker's honoraria from and serving as an advisory board member of MEDICE, Shire, and Novartis; and performing clinical trials for BMBF, Novartis, Vifor, and MEDICE. Dr Kis reported receiving speaker's honoraria from MEDICE, Servier, and Eli Lilly and Co; and serving as an advisory board member of MEDICE, Novartis, and Servier. Dr Huss reported serving as an advisory board member of Eli Lilly and Co, Engelhardt Arzneimittel, Janssen-Cilag, MEDICE, Novartis, Shire, and Steiner Arzneimittel within the past 5 years; serving as consultant to Engelhardt Arzneimittel, MEDICE, and Steiner Arzneimittel; receiving honoraria from Eli Lilly and Co, Engelhard Arzneimittel, Janssen-Cilag, MEDICE, Novartis, and Shire; and receiving unrestricted grants for investigator-initiated trials from Eli Lilly and Co, MEDICE, Engelhard Arzneimittel, and Steiner Arzneimittel. Mr Schlander reported receiving research support from sick funds, physicians' associations, health technology agencies, industry associations, and biopharmaceutical enterprises, including Janssen (Johnson & Johnson) and Shire, all under unrestricted educational grant policy. Dr Tebartz van Elst reported serving on advisory boards, giving lectures, or receiving travel grants within the last 3 years from Eli Lilly and Co, Janssen- Cilag, Novartis, Shire, UCB, GlaxoSmithKline, Servier, Janssen-Cilag, and Cyberonics. No other disclosures were reported" (Philipsen 2015). Furthermore: "Roland Fischer, MD, MEDICE Arzneimittel Pütter GmbH and Co KG, Iserlohn, Germany, gave advice on preparing the study protocol and assisted in managing serious adverse events; he received no compensation" (Philipsen 2015).

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Compas 2007 GPT *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	1. "Computer-based generation of randomization lists, prepacking, and shipment of medication were implemented by Medice Arzneimittel Pütter GmbH & Co. KG with a 1:1:1:1 treatment ratio, stratified by center and using blocks of variable length which were not communicated, to guarantee concealment" (Philipsen 2014).
Allocation concealment (selection bias)	Low risk	1. "Central randomization via fax is performed, using block randomization with variable block length. This guarantees concealment of randomization" (Philipsen 2010).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	1. "Matching placebo" (BfArM submission). 2. "For patients and therapists, the study is open with respect to the assignment to the two treatment conditions psychotherapy and clinical management. Blinding is restricted to medical treatment (methylphenidate, placebo) and observer ratings of symptoms of ADHD (CAARS-O-L) and clinical global impression. Raters are not informed on the treatment allocation and are not involved in the trial except of interviewing the subjects" (Philipsen 2010). 3. "Blinding was restricted to medication and to observer ratings of ADHD and CGI. We did not systematically assess whether blinding was effective in patients. However, because patients who received methylphenidate and those who received placebo both reported high numbers of AEs, with minimal effects to vital signs and weight, we believe the blinding was effective" (Philipsen 2015). 4. Stated not tested.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	1. "Matching placebo" (BfArM submission). 2. "For patients and therapists, the study is open with respect to the assignment to the two treatment conditions psychotherapy and clinical management. Blinding is restricted to medical treatment (methylphenidate, placebo) and observer ratings of symptoms of ADHD (CAARS-O-L) and clinical global impression. Raters are not informed on the treatment allocation and are not involved in the trial except of interviewing the subjects" (Philipsen 2010). 3. "Blinding was restricted to medication and to observer ratings of ADHD and CGI. We did not systematically assess whether blinding was effective in patients. However, because patients who received methylphenidate and those who received placebo both reported high numbers of AEs, with minimal effects to vital signs and weight, we believe the blinding was effective" (Philipsen 2015). 4. Stated not tested.
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Dropout rates at W52: methylphenidate 35 of 217 (16%), placebo 47 of 216 (22 %). 2. Dropouts due to adverse events: not clearly described. 3. Statistical method to account for missing data: Last Mean Carried Forward.
Selective reporting (reporting bias)	Low risk	1. Adverse event reporting threshold: All results (Author correspondence), published report (not reported), EUCTR (not reported), BfArM database (5 %). 2. Serious adverse events not reported in published report, on EUCTR or in BfArM database. Obtained from author correspondence. 3. Absence from work/school/education was reported as baseline-13 weeks, w13-w26 and w26-w52. However, baseline-52 weeks was not reported (BfArM database).

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Compas 2007 GPT *(Continued)*

Other bias	Low risk	None found.
Psychiatric comorbidity (External validity)	High risk	1. "Schizophrenia, bipolar disorder, borderline personality disorder, antisocial personality disorder, suicidal or self-injurious behaviour, autism, motor tics, Tourette's syndrome" (BfArM submission). 2. "Substance abuse/dependence within 6 months prior to screening. Episodic abuse is not an exclusion criterion. Positive drug screening" (BfArM submission). 3. "ADHD must be the predominant clinical feature in patients (major co-morbid conditions are excluded). Also patients with co-morbid conditions that clearly demand alternative treatment regimes or interfere with study medication are not included" (Philipsen 2010). 4. "Our findings may not be generalizable to routine care settings in which co-morbidities are not excluded and patients may have more psychosocial impairments or difficulties meeting the time and effort requirements for this trial" (Philipsen 2015).
Responder selection (External validity)	High risk	1. "Known methylphenidate intolerance" (BfArM submission). 2. Participants excluded at screening: MPH intolerance (n=1, 1.2%) (Philipsen 2014). 3. Particpants previously treated with a stimulant: 18 % (Table 6, Philipsen 2014). 4. Previous stimulant treatment: 90 of 419 (21%) (Table 1, Philipsen 2015).
Withdrawal effects (External validity)	High risk	1. Exclusion criteria: "Treatment with stimulants or ADHD-specific psychotherapy within 6 months prior the screening" (BfArM submission). 2. [excluded at pre-screening]: Current MPH treatment (n=39, 4.1%) (Philipsen 2010).

Casas 2008

Study characteristics	
Methods	**Trial ID(s)**: NCT00714688, 2007-002111-82 (EUCTR), 42603ATT3013 (protocol), 3013 (Regulatory reviews), LAMDA II (trial name). **Trial registry entry**: https://clinicaltrials.gov/ct2/show/NCT00714688. **Sponsor**: Janssen. **Funding/industry involvement**: Industry trial **Setting**: Europe. **No. sites**: 42 sites. **Start - completion**: Feb 2008 - April 2009. **Duration**: 13 weeks. **Sample size**: 279 participants. **Lead-in**: Not described.
Participants	*Information on exclusion criteria related to psychiatric comorbidity is listed in the risk of bias table.* **ADHD diagnostic system**: DSM IV - Text Revision. **Concomitant substance abuse diagnosis**: No. **Mean age (range)**: 36 years (18-64).

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Casas 2008 *(Continued)*

	Males (%): 52.
Interventions	**Trial arms**: 1. OROS methylphenidate 54 mg (n= 90) 2. OROS methylphenidate 72 mg (n= 92) 3. Placebo (n= 97) **Type of methylphenidate**: OROS methylphenidate. **Dosage**: 54 mg to 72 mg. **Fixed or titrated**: Fixed. **Administrations per day**: 1. **Co-intervention(s)**: Not described.
Outcomes	*Relevant outcomes are listed here.* 1. CAARS: Self short version (Self-rated, 26 items, 0-78 points) 2. CAARS-Observer: DSM IV Total ADHD (Investigator-rated, 18 Items, 0-54 points) 3. ADHD Impact Module – Adult (AIM-A): Overall quality of life (unspecified) 4. Cardiovascular variables 5. Harms
Notes	**Declared conflicts of interest**: "M. Casas has, in the past 3 years, been a consultant, a member of an advisory board and/or a speaker for Janssen–Cilag, Eli Lilly, Shire and Rubió. He has received research grants from Janssen–Cilag, Rubió and Eli Lilly. M. Rösler is a consultant for Janssen–Cilag, Medice, Lilly and Shire, and is a member of the speaker's bureau of Janssen–Cilag, Medice and Shire. J.J.S. Kooij has been a speaker for Janssen–Cilag BV and Eli Lilly and has received research grants from Janssen– Cilag BV and Shire. Y. Ginsberg has served as a consultant and speaker for Janssen–Cilag and Novartis and as a speaker for Lundbeck. She is a principal investigator for the LAMDA-I and LAMDA-II studies, funded by Janssen–Cilag. J.A. Ramos-Quiroga has, in the past 3 years, been a consultant, a member of an advisory board and/or a speaker for Janssen–Cilag, Eli Lilly, Shire and Rubió. He has received research grants from Jans- sen–Cilag, Rubió, Eli Lilly and Alicia Koplowitz Foundation. S. Heger is a former employee of Janssen–Cilag EMEA, and has since acted as a speaker and consultant for the company. J. Berwaerts is an employee of Johnson & Johnson Pharmaceutical Research & Development. J. Dejonkheere is a consultant working on behalf of SGS–Life Science Services, a company employed by Janssen–Cilag EMEA to provide statistical analysis. B. Schäuble and E. van der Vorst are employees of Janssen–Cilag EMEA" (Casas 2013).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	1. "Randomization was based on a computer-generated scheme prepared by the sponsor, balanced by using permuted blocks of treatments and stratified by study centre. Based on this scheme, study drug was packaged for each subject. Medication kit numbers were pre-printed on drug labels and assigned as subjects were randomly assigned to treatment. Treatment codes were obtained from a central interactive voice response system giving a medication kit number for the drug to which the subject had been assigned" (Casas 2013).
Allocation concealment (selection bias)	Low risk	1. "Randomization was based on a computer-generated scheme prepared by the sponsor, balanced by using permuted blocks of treatments and stratified by study centre. Based on this scheme, study drug was packaged for each subject. Medication kit numbers were pre-printed on drug labels and assigned as subjects were randomly assigned to treatment. Treatment codes were obtained from a central interactive voice response system giv-

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Casas 2008 *(Continued)*

		ing a medication kit number for the drug to which the subject had been assigned" (Casas 2013).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	1. "matching placebo. Placebo and PR OROS MPH were over-encapsulated to look identical" (CSR Synopsis). 2. Stated, not tested.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	1. "matching placebo. Placebo and PR OROS MPH were over-encapsulated to look identical" (CSR Synopsis). 2. Stated, not tested.
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Dropout rates: methylphenidate 72 of 182 (40 %), placebo 29 of 97 (30 %). 2. Dropouts due to adverse events: methylphenidate 34 of 72, placebo 2 of 29. 3. Statistical method used to account for missing data: Last observation carried forward (Casas, p. 270). 4. While only 55 partipants (59,8 %) allocated to 72 mg OROS MPH completed the study, 64,1% were considered to be "responders" (Casas 2013, p. 272). This was also noticed in the MHRA 2010 Review, p. 45: "The most appropriate method for handling missing data is to consider those that drop out as treatment failures. As noted earlier there is an incredibly high dropout rate in this study, with 30% of patients not completing in the placebo group, and 40% in the active group. It is clear from the data presented that in this trial the applicant has not treated missing as failure, as more patients appear to have responded than actually finished the trial in the 72 mg/day group".
Selective reporting (reporting bias)	Unclear risk	1. Adverse event reporting threshold: Published report (5%), CT.gov (5%), CSR synopsis (10%), AUS PI and MHRA PAR (1% combined Medori, Adler, Casas). 2. There were discepancies between the adverse event reporting in the MHRA Public Assessment Report between tables on page 60 and 62 for the outcomes of depression and aggression. 3. We do not know the actual adverse event reporting threshold for the trial in the pooled reporting in the Australian Prescribing Information, therefore we rated as unclear
Other bias	Unclear risk	None found.
Psychiatric comorbidity (External validity)	High risk	1. "any clinically unstable psychiatric condition; family history of schizophrenia or affective psychosis; autism, Asperger's syndrome, eating disorder, motor tics or history (including family history) of Tourette's syndrome; substance use disorder (not including caffeine or nicotine dependence)" (Casas 2013). 2. "In addition, as with many clinical trials in individuals with ADHD, the exclusion of subjects with clinically relevant comorbidities may mean that the patient cohort does not reflect the typical real- world ADHD population" (Casas 2013, p. 279).
Responder selection (External validity)	High risk	1. "Known to be a nonresponder to methylphenidate, or subject has a child known to be a nonresponder to methylphenidate" (EUCTR). 2. "Has been treated with any methylphenidatecontaining medication within 1 month of screening visit. One month is considered a reasonable time for patients treated with methylphenidate to return to a disease status baseline" (EUCTR). 3. "Participation in and premature withdrawal from 42603ATT3002 or 42603ATT3004 study" (EUCTR), which is the MEDORI trial. 4. "Known allergy or hypersensitivity to methylphenidate, or components of PR OROS methylphenidate" (EUCTR).

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Casas 2008 *(Continued)*

		5. "8.6 % [of the participants] stopped methylphenidate prior to randomisation" (MHRA PAR, p. 41).
Withdrawal effects (External validity)	High risk	1. "After up to 2 weeks' screening to enable safe tapering and discontinuation of disallowed medications (4 weeks for monoamine oxidase inhibitors), eligible subjects were randomly allocated (1:1:1) to OROS MPH 54 or 72 mg/day, or matching placebo" (Casas 2013). 2. "Concomitant medications to be discontinued during the screening period were α2 adrenergic receptor agonists, antipsychotics, theophylline, coumarin anticoagulants or anticonvulsants, any ADHD treatment, monoamine oxidase inhibitors, herbal and over-the-counter stimulant diet preparations or drugs containing stimulants" (Casas 2013). 3. "[Exclusion criteria] Has been treated with any methylphenidatecontaining medication within 1 month of screening visit. One month is considered a reasonable time for patients treated with methylphenidate to return to a disease status baseline" (EUCTR). 4. "8.6 % stopped methylphenidate prior to randomisation" (MHRA PAR, p. 41)

Retz 2008

Study characteristics	
Methods	**Trial ID(s)**: NCT00730249, 2008-000942-29 (EUCTR), 6520-0650-13 (protocol), QUMEA (trial name). **Trial registry entry**: https://clinicaltrials.gov/ct2/show/NCT00730249. **Sponsor**: Medice. **Funding/industry involvement**: Industry trial. **Country**: Germany. **No. trial sites**: 11 sites. **Start - completion**: Sep 2008 - Jan 2010. **Duration**: 8 weeks. **Sample size**: 162 participants.
Participants	*Information on exclusion criteria related to psychiatric comorbidity is listed in the risk of bias table.* **ADHD diagnostic system**: DSM IV. **Concomitant substance abuse diagnosis**: No. **Mean age (range)**: 37 years (18 +) **Males** (%): 47.
Interventions	**Trial arms**: 1. Extended-release methylphenidate (n= 84) 2. Placebo (n= 78) **Type of methylphenidate**: Extended-release methylphenidate **Dosage range**: 40 mg to 120 mg. **Fixed or titrated**: Titrated. **Administrations per day**: 2. **Co-intervention(s)**: Disease management sessions (6 sessions).

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Retz 2008 *(Continued)*

Outcomes	*Relevant outcomes are listed here.* 1. CAARS: Long Version (Self-rated, 66 items, 0-90 points) 2. Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS) (Investigator-rated, 7 domains, 28 items. Range: 0 - 56) 3. Cardiovascular variables 4. Harms
Notes	**Declared conflicts of interest**: "WR has received honoraria and travel grants from Novartis, AstraZeneca, Medice and Flynn Pharma and is on the advisory board of Shire. MR has received honoraria, travel grants, and paid consul- tancy from Lilly, Janssen-Cilag, Shire and Medice and is on the advisory board of Lilly and Shire. CO has received honoraria from Medice. AS currently serves as trial statistician is on a data safety and monitoring the advisory board for Boehringer Ingelheim KG. BA is on the advisory board of Lilly. AP has received honoraria and travel grants from Janssen-Cilag, Medice, Lilly, Novartis and is on the advisory board of Janssen-Cilag, Lilly and Shir. RF is the Medical Director of Medice. RA is member of the general management of Medice and sponsor of the trial" (Retz 2012).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	1. "Randomisation was performed by Medice's Galenic Department which included the generation of the randomisation list and the preparation of emergency envelopes. We used block randomisation with a block size of 4. The block size was not mentioned in the investigational plan or the consent given to patients" (Retz 2012).
Allocation concealment (selection bias)	Low risk	1. "Randomisation was performed by Medice's Galenic Department which included the generation of the randomisation list and the preparation of emergency envelopes. We used block randomisation with a block size of 4. The block size was not mentioned in the investigational plan or the consent given to patients" (Retz 2012)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	1. "double-blind, placebo-controlled". 2. Stated, not tested.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	1. "double-blind, placebo-controlled". 2. Stated, not tested
Incomplete outcome data (attrition bias) All outcomes	Low risk	1. Dropout rates: methylphenidate 4 of 84 (5 %), placebo 3 of 78 (4 %). 2. Dropouts due to adverse events: methylphenidate 3 of 4, placebo 1 of 3. 3. Statistical method to account for missing data: LOCF (primary outcome), not clear for secondary outcomes.
Selective reporting (reporting bias)	High risk	1. Adverse event reporting threshold: Published paper (only 12 events reported and they had to occur statistically significant more often in either arm, 17 % level for MPH) 2. Adverse events leading to dropout and dose reductions not reported.
Other bias	High risk	1. Baseline differences; more women in the MPH ER group than the placebo group (61 % vs 44 %) and baseline CAARS-Self rating (126 points vs 114 points), despite a sample size of 162 participants.
Psychiatric comorbidity (External validity)	High risk	1. "Individuals with low intelligence (IQ <85), dementia, schizophrenia, bipolar disorder, current major depression, acute anxiety disorders and other unsta-

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Retz 2008 *(Continued)*

		ble psychiatric conditions were excluded, as were subjects with any serious medical illness" (Retz 2012). 2. "Also subjects with drug or alcohol dependence during the 6 months before screening [...] were not included" (Retz 2012).
Responder selection (External validity)	High risk	1. Previous ADHD treatment: 29.8% in the MPH ER group and 37.2% in the placebo group (Retz 2012).
Withdrawal effects (External validity)	High risk	1. "Treatment with psychostimulants in the past two weeks before screening" (CT.gov). 2. "A wash-out period of at least 2 weeks was necessary for any psychopharmacological drug before study inclusion" (Retz 2012) 3. Previous stimulant treatment: 29.8 % in the MPH ER group and 37.2 % in the placebo group (Retz 2012).

College Study 2009

Study characteristics	
Methods	**Trial ID(s)**: NCT00931398, ConcertaATT4100. **Trial registry entry**: https://clinicaltrials.gov/ct2/show/NCT00931398. Sponsor: University of Pittsburg **Funding/industry involvement**: Ortho-McNeil-Janssen was involved in the study (listed on ClinicalTrials.gov as collaborator). **Country**: United States. **No. sites**: 1. **Start - completion**: "Study was not initiated due to lack of funding by the sponsor" according to CT.gov entry. **Duration**: 8 weeks. **Sample size**: No data.
Participants	*Information on exclusion criteria related to psychiatric comorbidity is listed in the risk of bias table.* **ADHD diagnostic system**: DSM IV. **Concomitant substance abuse diagnosis**: No. **Mean age (range)**: No data (range 18 to 25). **Males** (%): No data.
Interventions	**Trial arms**: 1. OROS methylphenidate 2. Placebo **Type of methylphenidate**: OROS methylphenidate. **Dosage range**: 18 mg to 72 mg. **Fixed or titrated**: No data. **Administrations per day**: No data. **Co-intervention(s)**: No data.

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College Study 2009 *(Continued)*

Outcomes	*Relevant outcomes are listed here.* Study was not conducted. It should assess college students' performance, such as achieved grade point average
Notes	**Declared conflicts of interest**: No publications or published protocols.

Goodman 2009

Study characteristics	
Methods	**Trial ID(s)**: NCT00937040, CONCERTAATT3014 (protocol), CR015058. **Trial registry entry**: https://clinicaltrials.gov/ct2/show/NCT00937040. **Sponsor**: Ortho-McNeil Janssen. **Funding/industry involvement**: Industry trial. **Country**: United States. **No. sites**: 35 sites. **Start - completion**: July 2009 - Feb 2010. **Duration**: 6 weeks. **Sample size**: 357
Participants	*Information on exclusion criteria related to psychiatric comorbidity is listed in the risk of bias table.* **ADHD diagnostic system**: DSM IV. **Concomitant substance abuse diagnosis**: No. **Mean age (range)**: 36 years (18-65) **Males** (%): 54.
Interventions	**Trial arms**: 1. OROS methylphenidate (n= 178) 2. Placebo (n= 179) **Type of methylphenidate**: OROS methylphenidate. **Dosage range**: 18 mg to 72 mg. **Fixed or titrated**: Titrated. **Administrations per day**: 1. **Co-intervention(s)**: Not described.
Outcomes	*Relevant outcomes are listed here.*
Notes	**Declared conflicts of interest**: "Dr Goodman discloses the following financial considerations: consultant and/or reports associated with WebMD, Medscape, Temple University, American Professional Society of ADHD and Related Disorders, Neuroscience Education Institute, Children and Adults with ADHD Association, Shire, McNeil, Cephalon, Teva, Lundbeck, Janssen US and Canada, OptumInsight (Ingenix Pharmaceutical Services), Sunovion, Thomson Reuters, GuidePoint Global, Otsuka, Med-IQ, Novartis, Ironshore Pharmaceuticals, Neos Therapeutics, Rhodes Pharmaceuticals, Avacat, Major League Baseball, National Football League, American Physician Institute for Advanced Professional Studies, LLC, Healthequity Corporation, Prescriber's Letter, Consumer Reports, and Pontifax. Dr Rostain is an em-

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Goodman 2009 *(Continued)*

ployee of the University of Pennsylvania; has been on the scientific advisory boards of Pearson and Alcobra; has been a consultant to the State University of New York (SUNY) at Albany; has received grant/research support from the Agency for Healthcare Research and Quality and the National Institute of Mental Health; has made educational presentations/received honoraria from WebMD, MedScape, and the National Association for Continuing Education; and has received royalties from Routledge/Taylor Francis Group. Dr Armstrong discloses the following financial considerations relating to Johnson & Johnson: stockholder, stock options holder, and pension. Dr Ma is an employee of Johnson & Johnson Consumer, Inc, and is a Johnson & Johnson stockholder. Dr Ascher is an employee of Janssen Pharmaceutical Development, LLC, and is a stockholder of Johnson & Johnson as well as a holder of stock options. Dr Starr is an employee of Janssen Scientific Affairs, LLC, and is a Johnson & Johnson stockholder" (Goodman 2016).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	1. "Subjects were randomly assigned by an interactive voice response system to 18 mg/d of OROS methylphenidate or matching placebo" (Goodman 2016).
Allocation concealment (selection bias)	Low risk	1. "Subjects were randomly assigned by an interactive voice response system to 18 mg/d of OROS methylphenidate or matching placebo" (Goodman 2016).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	1. "OROS methylphenidate or matching placebo" (Goodman 2016). 2. "Treatment dose could be increased at each of 3 subsequent weekly visits to 36 mg, 54 mg, and 72 mg (maximum) until the subject reached an AISRS score < 18 or a limit of tolerability" (Goodman 2016). 3. "After the investigator completed the AISRS and CGI-I assessments at each DAP visit, the investigator determined the subject's daily dose. The dose was maintained or adjusted up or down by 18-mg steps, but the adjusted daily dose was not allowed by protocol to go below 18 mg/d or above 72 mg/d. At Visit 5, no dose increase was allowed" (CSR synopsis). 4. Stated, not tested.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	1. "OROS methylphenidate or matching placebo" (Goodman 2016). 2. "Treatment dose could be increased at each of 3 subsequent weekly visits to 36 mg, 54 mg, and 72 mg (maximum) until the subject reached an AISRS score < 18 or a limit of tolerability" (Goodman 2016). 3. "After the investigator completed the AISRS and CGI-I assessments at each DAP visit, the investigator determined the subject's daily dose. The dose was maintained or adjusted up or down by 18-mg steps, but the adjusted daily dose was not allowed by protocol to go below 18 mg/d or above 72 mg/d. At Visit 5, no dose increase was allowed" (CSR synopsis). 4. Stated, not tested.
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Dropout rates: methylphenidate 37 of 178 (21 %), placebo 41 of 179 (23 %). 2. Dropouts due to adverse events: methylpehnidate 8 of 37, placebo 5 of 41. 3 3. Statistical method used to account for missing data: Last observation carried forward.
Selective reporting (reporting bias)	High risk	1. Adverse event reporting thresholds: CT.gov (5% for methylphenidate arm), published paper (5%), clinical study report synopsis (not systematically reported). 2. Cardiovascular variables and weight were measured but not reported (CSR synopsis, p. 6).

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Goodman 2009 *(Continued)*

		3. AIM-A overall quality of life score not reported (like in Casas 2008), only subscales (Goodman 2016).
Other bias	Low risk	None found.
Psychiatric comorbidity (External validity)	High risk	1. "History of diagnosis of substance or alcohol dependence or admission/hospitalization for rehabilitation for dependence. Current neurologic or psychiatric diagnosis that would make patient inappropriate for participation. Anxiety assessments of moderate or severe. Depression assessments of moderate or severe" (CT.gov).
Responder selection (External validity)	High risk	1. "Known allergies, hypersensitivity, or intolerance to OROS MPH" (CT.gov). 2. "Subjects who were unable to tolerate 18 mg daily were discontinued from the study" (CSR synopsis).
Withdrawal effects (External validity)	Low risk	1. "Subjects excluded were those with [...] a history of stimulants or atomoxetine use within 5 years or other ADHD medications within 30 days and those for whom, in the investigator's opinion, methylphenidate posed an unacceptable risk through a potential drug interaction or a concurrent medical, neurologic, or psychiatric illness" (Goodman 2016). 2. "None of the subjects was currently taking medication for ADHD" (Goodman 2016).

Weisler 2009

Study characteristics	
Methods	**Trial ID(s)**: NCT00880217, 31001074ATT2001 (protocol), CR015964. **Trial registry entry**: https://clinicaltrials.gov/ct2/show/NCT00880217. **Sponsor**: Janssen. **Country**: United States. **No. trial sites**: 37 sites. **Start - completion**: May 2009 - Jan 2010. **Duration**: 6 weeks. **Sample size**: 216 (For the methylphenidate, atomoxetine and placebo arms).
Participants	*Information on exclusion criteria related to psychiatric comorbidity is listed in the risk of bias table.* **ADHD diagnostic system**: DSM IV - Text Revision. **Concomitant substance abuse diagnosis**: No. **Mean age (range)**: 33 years (18-55) **Males** (%): 62.
Interventions	**Trial arms**: 1. OROS methylphenidate 54 mg/day (n= 68) 2. atomoxetine 80 mg/day (n= 74) 3. Placebo (n= 74) 4. bavisant 1 mg/day (not included) 5. baviant 3 mg/day (not included) 6. bavisant 10 mg/day (not included)

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Weisler 2009 *(Continued)*

Type of methylphenidate: OROS methylphenidate.
Dosage range: 54 mg.

Fixed or titrated: Fixed.

Administrations per day: 1.

Co-intervention(s): Not described.

Outcomes	*Relevant outcomes are listed here.* 1. CAARS:DSM IV total ADHD (Self-rated, 18 items, 0-54 points) 2. Attention Deficit Hyperactivity Rating Scale, Investigator-Administered and Scored Version (ADHD RS) (investigator-rated, 18 items, 0-54 points) 3. Harms
Notes	**Declared conflicts of interest**: "Richard Weisler was the principal investigator for the study and received no compensation for time spent in the preparation of this manuscript. Dr Weisler has been a consultant to, on the speaker's bureaus of, and received research support from Johnson & Johnson or an operating company (McNeil Pharmaceutical, Janssen). He owns Johnson & Johnson stock in mutual funds or in managed accounts with no direct control. Richard Weisler, MD, in his career, has also been a consultant to, on the speaker's bureaus of, and/or received research support from the following: Abbott, speaker's bureau, consultant, received research support; Agency for Toxic Substances and Disease Registry, consultant; Astra Zeneca, speaker's bureau, consultant, received research support; Biovail, speaker's bureau, consultant, received research support; Bristol-Myers Squibb, speaker's bureau, consultant, received research support, stockholder has held or holds stock; Burroughs Wellcome, speaker's bureau, received research support; Cenerx, received research support; Centers of Disease Control and Prevention, consultant; Cephalon, speaker's bureau, consultant, received research support; Ciba Geigy, speaker's bureau, received research support; CoMentis, received research support; Corcept, consultant, Cortex, stockholder has held or holds stock; Dainippon Sumitomo Pharma America, received research support; Eisai, received research support; Eli Lilly, speaker's bureau, consultant, received research support; Forest, speaker's bureau, consultant, received research support; GlaxoSmithKline, speaker's bureau, consultant, received research support; Lundbeck, received research support; Medicinova, received research support; Medscape Advisory Board, consultant; Merck, received research support, stockholder has held or holds stock; National Institute of Mental Health, consultant, received research support; Neurochem, received research support; New River Pharmaceuticals, received research support; Novartis, speaker's bureau, received research support; Organon, speaker's bureau, consultant, received research support; Otsuka America Pharma, consultant; Pfizer, speaker's bureau, consultant, received research support, stockholder has held or holds stock; Pharmacia, consultant, received research support; Repligen, received research support; Saegis, received research support; Sandoz, received research support; Sanofi, speaker's bureau, consultant, received research support; Sanofi- Synthelabo, speaker's bureau, consultant, received research support; Schwabe/Ingenix, received research support; Sepracor, received research support; Shire, speaker's bureau, consultant, received research support; Solvay, speaker's bureau, consultant; Sunovion, speaker's bureau, consultant, received research support; Synaptic, received research support; Takeda, received research support; TAP, received research support; Transcept Pharma, consultant, received research support; TransTech, consultant; UCB Pharma, received research support; Validus, speaker's bureau, consultant; Vela, received research support; and Wyeth, speaker's bureau, consultant, received research support. Gahan Pandina, Ella Daly, Kimberly Cooper and Cristi- ana Gassmann-Mayer are employees of Janssen Research & Development, LLC, and own stock in Johnson & Johnson. All authors met International Committee of Medical Journal Editors (ICMJE) criteria and all those who fulfilled those criteria are listed as authors. Bradford Challis, an employee of Janssen Research & Development, LLC, contributed to writing of the initial draft with author guidance, copy editing and incorporating author comments. The study is registered at ClinicalTrials.gov: NCT00880217" (Weisler 2012).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	1. "Participants were randomly assigned equally to one of six treatment groups" (Weisler 2012).

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Weisler 2009 *(Continued)*

		2. "The randomization scheme was based on a computer-generated schedule, balanced by using permuted blocks of treatments, stratified by centre and implemented using an interactive voice response system" (Weisler 2012).
Allocation concealment (selection bias)	Low risk	1. "The randomization scheme was based on a computer-generated schedule, balanced by using permuted blocks of treatments, stratified by centre and implemented using an interactive voice response system" (Weisler 2012).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	1. "The blinding of the study medication was achieved by over-encapsulation, with all study drugs provided as opaque hard-gelatin capsules that were identical in shape, size, and appearance" (Weisler 2012).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	1. "The blinding of the study medication was achieved by over-encapsulation, with all study drugs provided as opaque hard-gelatin capsules that were identical in shape, size, and appearance" (Weisler 2012).
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Dropout rates: methylphenidate 13 of 68 (19 %), placebo 11 of 74 (15 %). 2. Dropouts due to adverse events: methylphenidate 6 of 13, placebo 2 of 11. 3. Statistical method to account for missing data: mixed effects model, but unclear how it was used.
Selective reporting (reporting bias)	High risk	1. Adverse event reporting threshold: Published report (5 %, except cardiovascular events where they reported to 2 %). 2. Cardiovascular variables measured but not reported.
Other bias	Low risk	None found.
Psychiatric comorbidity (External validity)	High risk	1. "[Exclusion criteria] Patients with any current Axis I psychiatric disorder" (CT.gov). 2. "The main exclusion criteria were any current Axis I psychiatric condition including major depressive disorder, bipolar disorder, schizophrenia, generalized anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, borderline personality disorder, or eating disorder" (Weisler 2012).
Responder selection (External validity)	High risk	1. "Demonstrated history of non-response to treatment with a psychostimulant medication or to treatment with atomoxetine or methylphenidate" (Weisler 2012). 2. "The percentage of participants who took psychotropic medication in the 3 months prior to study treatment ranged from 7 % to 14 % among the treatment groups" (Weisler 2012).
Withdrawal effects (External validity)	Unclear risk	1. "The percentage of participants who took psychotropic medication in the 3 months prior to study treatment ranged from 7 % to 14 % among the treatment groups" (Weisler 2012). 2. Previous stimulant use and wash-out of current stimulants not described.

Huss 2010

Study characteristics	
Methods	**Trial ID(s)**: NCT01259492, 2010-021533-31 (EUCTR), CRIT124D2302 (protocol), D2302 (regulatory reviews). **Trial registry entry**: https://clinicaltrials.gov/ct2/show/NCT01259492. **Sponsor**: Novartis.

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Huss 2010 *(Continued)*

	Funding/industry involvement: Industry trial **Setting**: Belgium, Sweden, Denmark, Germany, Norway, Columbia, South Africa, USA, and Singapore. **No. sites**: 67 sites. **Start - completion**: Nov 2012 - Aug 2012. **Duration**: 9 weeks. **Sample size**: 725 participants.
Participants	*Information on exclusion criteria related to psychiatric comorbidity is listed in the risk of bias table.* **ADHD diagnostic system**: DSM IV. **Concomitant substance abuse diagnosis**: No. **Mean age (range)**: 35 years (18-60) **Males** (%): 55.
Interventions	**Trial arms**: 1. MPH LA 40 mg (n= 181) 2. MPH 60 mg (n= 182) 3. MPH 80 mg (n= 181) 4. Placebo (n= 181) **Type of methylphenidate**: Long-acting methylphenidate **Dosage**: 40 mg to 80 mg. **Fixed or titrated**: Fixed. **Administrations per day**: 1. **Co-intervention(s)**: "Any psychological or behavioral therapies for the treatment of ADHD were discontinued at least 1 month prior to the screening visit. Patients who initiated these therapies within 3 months prior to screening visit for reasons other than ADHD were excluded from the trial." (Huss 2014)
Outcomes	*Relevant outcomes are listed here.* 1. Adult Self-Report-Scale (ASRS) (Self-rated, 18 items, 0-72 points) 2. ADHD DSM-IV RS (Investigator-rated, 18 items, 0-54 points) 3. CAARS:Observer ("assessments made by a friend, family member or colleague", 26 items, 0-78 points) 4. Harms
Notes	**Declared conflicts of interest**: "Michael Huss has served as an advisory board member for Eli Lilly, Engelhardt Arzneimittel, Janssen-Cilag, Medice, Novartis, Shire, and Steiner Arzneimittel, and as a consultant for Engelhardt Arzneimittel, Medice, and Steiner Arzneimittel. He received honoraria from Eli Lilly, Engelhardt Arzneimittel, Janssen-Cilag, Medice, Novartis, and Shire. He has received unrestricted grants for investigator-initiated trials from Eli Lilly, Medice, Engelhardt Arzneimittel, and Steiner Arzneimittel. Ylva Ginsberg has served as a consultant and speaker for Janssen-Cilag and Novartis and as a speaker for Lundbeck. She has also been a principal investigator of two international multicenter trials initiated by Janssen-Cilag, and she was the coordinating investigator of a MPH trial conducted in adult prison inmates with ADHD, funded by the Swedish Ministry of Health and Social Affairs. Torbjorn Tvedten has received speaker fees from Novartis and Lundbeck. Torben Arngrim has been involved in clinical trials conducted by Janssen-Cilag and Novartis. He has received speaker fees from Janssen-Cilag, Novartis, Eli Lilly, and HB Pharma, and has served as an advisory board member for Novartis and Shire. Alexandra Philipsen has received speaker fees and/or travel grants from Eli Lilly, Janssen-Cilag, Medice, Novartis, and Shire, and has been involved in clinical trials conducted by Eli Lilly, Janssen-Cilag, Medice, and Novartis. She has served as an advisory board member for Eli Lilly, Janssen-Cilag, Medice, Novartis, and Shire. She is the co-ordinating investigator of a multicenter trial on the treatment of adult ADHD (Current Controlled Trials ISRCTN54096201, funded by the Federal Ministry of Education

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Huss 2010 *(Continued)*

and Research 01GV0606). Katherine Carter is an employee of Novartis Pharmaceutical Corporation. Chien- Wei Chen is an employee of Novartis Pharmaceutical Corporation. Vinod Kumar is an employee of Novartis Pharmaceutical Corporation" (Huss 2014).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	1. "Patients were randomized to one of the treatment arms using a validated Interactive Voice/Web Response System (IVRS/ IWRS). A unique, confidential randomization number was assigned to each patient and IVRS/ IWRS allocated medication accordingly, as assigned, throughout the respective treatment periods. An unbiased, confidential patient randomization list was produced by the IVRS/ IWRS provider using a validated system that automated the random assignment of patient numbers to randomization numbers. A separate medication randomization list was produced under the responsibility of Novartis Drug Supply Management using a validated system that automated the random assignment of medication numbers to medication packs containing each of the study drugs" (Huss 2014).
Allocation concealment (selection bias)	Low risk	1. "Patients were randomized to one of the treatment arms using a validated Interactive Voice/Web Response System (IVRS/ IWRS). A unique, confidential randomization number was assigned to each patient and IVRS/ IWRS allocated medication accordingly, as assigned, throughout the respective treatment periods. An unbiased, confidential patient randomization list was produced by the IVRS/ IWRS provider using a validated system that automated the random assignment of patient numbers to randomization numbers. A separate medication randomization list was produced under the responsibility of Novartis Drug Supply Management using a validated system that automated the random assignment of medication numbers to medication packs containing each of the study drugs" (Huss 2014).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	1. "All sites and personnel for clinical, medical, statistical, data management and monitoring were blinded, and randomization data were kept strictly confidential until the time of un-blinding after the conclusion of the study. The identity of the treatments has been concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, taste, and odor, in line with Consort guidelines". 2. Stated not tested.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	1. "All sites and personnel for clinical, medical, statistical, data management and monitoring were blinded, and randomization data were kept strictly confidential until the time of un-blinding after the conclusion of the study. The identity of the treatments has been concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, taste, and odor, in line with Consort guidelines" (Huss 2014). 2. "Patients whose symptoms were not adequately controlled on study medication were discontinued from the study and treated at the discretion of the investigator" (Huss 2014). 3. Stated not tested.
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Dropout rates: methylphenidate 113 of 544 (21 %), placebo 28 of 181 (16 %). 2. "All data for the 22 patients randomized at one site were removed fro the efficacy analysis due to serious non-compliance with International Conference On Harmonization (ICH)-GCP at the site" (MEB, p. 24). 3. Dropouts due to adverse events: methylphenidate 61 of 113 (11 %) and placebo 4 of 28 (2 %) (CTR, p. 40). 4. Statistical method to account for missing data: Last observation carried forward.

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Huss 2010 *(Continued)*

		5. For the DSM IV RS outcome, there were more "responders" than actual responders in two of the three methylphenidate arms: 60 mg, completers 141/182 (77 %) and 80 mg 138/181 (76 %), compared to 80,5 % and 81 % completers (Huss 2014, p. 53)
Selective reporting (reporting bias)	High risk	1. Adverse event reporting threshold: Published report (5 %), CT.gov (2 %, data was pooled from the 3 phases), Novartis trial report (5 %, although the report also reported adverse events adjusted for exposure time with a threshold of 1 event per 100 patient weeks). 2. Blood pressure and pulse from phase 1 not reported. 3. Reporting threshold for adverse events leading to dropout: published report (2 %), Clinical Trial Report (0,4 % corresponding to two participants) CTR, p. 40.
Other bias	Low risk	None found.
Psychiatric comorbidity (External validity)	High risk	1. "Any psychiatric condition that requires medication or may interfere with study participation" (Clinical trial report). 2. "A limitation of the study is the limited external validity, as the protocol did not allow the inclusion of patients with psychiatric co-morbidities" (Huss 2014, p. 61)
Responder selection (External validity)	High risk	1. "Additionally, patients with either hypersensitivity or history of poor response or intolerance to stimulants as per the investigator's judgment were excluded from this study" (Huss 2014). 2. "13.3% of the patients had received stimulants previously, most frequently used treatments were MPH/ methylphenidate (9.1%), mixed amphetamine salts (2.5%), and lisdexamfetamine dismesylate (1.1%)" (Huss 2014).
Withdrawal effects (External validity)	High risk	1. "Any therapies for ADHD, as well as all psychotropic medications were required to be discontinued 1–4 weeks prior to randomization" (Huss 2014) 2. "In patients receiving any psychotropic medications the minimum discontinuation period varied according to drug class as follows: 1 week prior to the screening visit for stimulants including MPH, antidepressants other than fluoxetine, antipsychotics, anticonvulsants for non- epilepsy uses, mood stabilizing medications such as lithium, and herbal preparations with psychotropic potential" (Huss 2014). 3. "13.3% of the patients had received stimulants previously, most frequently used treatments were MPH/ methylphenidate (9.1%), mixed amphetamine salts (2.5%), and lisdexamfetamine dismesylate (1.1%)" (Huss 2014).

Takahashi 2011

Study characteristics	
Methods	**Trial ID(s)**: NCT01323192, JNS001-JPN-A01 (protocol), CR017755. **Trial registry entry**: https://clinicaltrials.gov/ct2/show/NCT01323192. **Sponsor**: Janssen. **Funding/industry involvement**: Industry trial **Setting**: Japan. **No. sites**: 39 sites. **Start - completion**: March 2011 - April 2012. **Duration**: 8 weeks. **Sample size**: 284

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Participants	*Information on exclusion criteria related to psychiatric comorbidity is listed in the risk of bias table.* **ADHD diagnostic system**: DSM IV - Text Revision. **Concomitant substance abuse diagnosis**: No. **Mean age (range)**: 34 years (18-59) **Males** (%): 49
Interventions	**Trial arms**: 1. OROS methylphenidate (n= 143) 2. Placebo (n= 141) **Type of methylphenidate**: OROS methylphenidate **Dosage range**: 18 mg to 72 mg **Fixed or titrated**: Titrated. **Administrations per day**: 1. **Co-intervention(s)**: Not described.
Outcomes	*Relevant outcomes are listed here.* 1. CAARS: DSM-IV total ADHD (Self-rated, 18 items, 0-54 points) 2. CAARS: DSM IV total ADHD symptoms (Investigator-rated, 18 items, 0- 54 points) 3. Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-QSF) (Self-rated, 14 items, 14-70 points) 4. Cardiovascular variables 5. Harms
Notes	**Declared conflicts of interest**: "NT, TK, YT, YS, YK and TM are employees of Janssen Pharmaceutical KK, Japan. This study was supported by Janssen Pharmaceu- tical KK, Japan. Editorial support was provided by Allison Michaelis, PhD, of Medergy and was funded by Janssen Global Services, LLC" (Takahashi 2014).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	1. "Patients were randomly assigned to receive OROS MPH or placebo based on a computer-generated randomization schedule prepared before the study by the sponsor or under the supervision of the sponsor. The randomization was balanced by using randomly permuted blocks of treatment and was stratified by study centre. Study drug code numbers were preprinted on the study drug labels and were assigned to patients as they qualified for the study and were randomly assigned to treatment" (Takahashi 2014).
Allocation concealment (selection bias)	Low risk	1. "To maintain the study blind, the study drug container had a multipart label containing the protocol number, medication kit number, code number and other information on each part. It was impossible to identify the study drug by using the label information" (Takahashi 2014).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	1. "The study drugs were identical in appearance and were packaged in identical containers. Data that may potentially unblind the treatment assignment (e.g., study agent serum concentrations) were to be handled with special care to ensure that the integrity of the blind was maintained and the potential for bias was minimized. This could include making special provisions, such

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Takahashi 2011 *(Continued)*

		as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of data- base lock and unblinding" (Takahashi 2014). 2. The pills had different colours according to their strength (yellow, grey, white) (CSR Synopsis). 3. Stated, not tested.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	1. "The study drugs were identical in appearance and were packaged in identical containers. Data that may potentially unblind the treatment assignment (e.g., study agent serum concentrations) were to be handled with special care to ensure that the integrity of the blind was maintained and the potential for bias was minimized. This could include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of data- base lock and unblinding" (Takahashi 2014). 2. The pills had different colours according to their strength (yellow, grey, white) (CSR Synopsis). 3. Stated, not tested.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1. Dropout rates: methylphenidate 9 of 143 (6 %), placebo 6 of 141 (4 %). 2. Dropouts due to adverse events: methylphenidate 6 of 9, placebo 1 of 6. 3. Statistical method used to account for missing data: Last observation carried forward (for efficacy analyses).
Selective reporting (reporting bias)	High risk	1. Adverse event reporting threshold: Published paper (5 %), Clinical Study Report synopsis (5 %), CT.gov (2 %). 2. No systematic reporting of adverse events from the post-study visit. 3. Blood pressure and weight not reported, only mean change for pulse was reported, but not SD (CSR synopsis).
Other bias	Low risk	None found.
Psychiatric comorbidity (External validity)	High risk	1. "Exclusion criteria included diagnosis of bipolar I disorder, schizophrenia, schizoaffective disorder, severe obsessive compulsive disorder, pervasive developmental disorder (e.g., autistic disorder or Asperger's disorder) or suicidality" (Takahashi 2014). 2. "Patients with confirmed cancer or other serious illnesses (e.g., hepatic or renal insufficiency or significant cardiac, gastrointestinal, psychiatric, or metabolic disturbances) were also excluded" (Takahashi 2014). 3. "Third, ADHD is more likely to be complicated with other psychiatric illness, such as anxiety disorders. We excluded these patients in this study, and the efficacy of OROS MPH for these patients should be tested in the future" (Takahashi, p. 498)
Responder selection (External validity)	High risk	1. "Patients were excluded from the study if they were a non-responder to MPH and/or had a history of hypersensitivity or intolerance to MPH" (Takahashi 2014). 2. "It could be considered that excluding non-responders to MPH from this study may have had a positive bias on patient selection. However, no patient was excluded from the study due to this exclusion criterion, so it is unlikely that this exclusion had an effect on the overall results" (Takahashi 2014, p. 498). 3. "14.7% (OROS MPH) and 12.1% (placebo) received one or more psychotropic agents for ADHD within 3 months prior to screening" (Takahashi 2014).
Withdrawal effects (External validity)	High risk	1. "Washout up to 4 weeks of ADHD medication" (Takahashi 2014), CT.gov and CSR Synopsis says 1-2 weeks.

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Takahashi 2011 *(Continued)*

2. "Within 3 months prior to screening, 14.7% subjects in the JNS001 group and 12.1% subjects in the placebo group received 1 or more psychotropic agents for ADHD. The most commonly used psychotropic agents for ADHD were atomoxetine hydrochloride and pemoline" (CSR Synopsis).

Foquest 2014

Study characteristics	
Methods	**Trial ID(s)**: NCT02139124, 063-010 (protocol). **Trial registry entry**: https://clinicaltrials.gov/ct2/show/NCT02139124. **Sponsor**: Purdue. **Funding/industry involvement**: Industri trial **Setting**: United States and Canada. **No. sites**: 38 sites. **Start - completion**: Oct 2014 - Jan 2015. **Duration**: 4 weeks. **Sample size**: 375 participants.
Participants	*Information on exclusion criteria related to psychiatric comorbidity is listed in the risk of bias table.* **ADHD diagnostic system**: DSM V. **Concomitant substance abuse diagnosis**: No. **Mean age (range)**: 36 (years 18 - 72) **Males** (%): 47.
Interventions	**Trial arms**: 1. methylphenidate 25 mg (n= 77) 2. methylphenidate 45 mg (n= 73) 3. methylphenidate 70 mg (n= 73) 4. methylphenidate 100 mg (n= 74) 5. Placebo (n= 78) **Type of methylphenidate**: Controlled-release methylphenidate. **Dosage**: 25 mg to 100 mg. **Fixed or titrated**: Fixed. **Administrations per day**: Not described. **Co-intervention(s)**: Not described.
Outcomes	*Relevant outcomes are listed here.* 1. ADHD-5-RS Total Score (Investigator-rated, 18 items, 0-54 points) 2. Harms
Notes	**Declared conflicts of interest**: No publication available, data from ClinicalTrials.gov and regulatory documents.
Risk of bias	

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Foquest 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	1. "This study is a randomized, phase III, multicenter, placebo-controlled […]" (CT.gov).
Allocation concealment (selection bias)	Unclear risk	1. Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	1. "placebo-controlled" (CT.gov). 2. "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)" (CT.gov). 3. Stated, not tested.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	1. "placebo-controlled" (CT.gov). 2. "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)" (CT.gov). 3. Stated, not tested.
Incomplete outcome data (attrition bias) All outcomes	High risk	1. Dropout rates: methylphenidate 33 of 297 (11 %), placebo 9 of 78 (12 %). 2. Dropouts due to adverse events: methylphenidate 8 of 33, placebo 2 of 9. 3. Statistical method to account for missing data: not described.
Selective reporting (reporting bias)	High risk	1. SAE uncertainties. Health Canada Monograph reports only five events but four of these events do no appear on CT.gov or in FDA's review. On CT.gov it says 16 events in 12 participants and in FDA Clinical Review 12 participants are reported (but events not specified). 2. Adverse event reporting threshold: No threshold on CT.gov (0 %), Canada Health Product Monograph (1 %), FDA Clinical Review (2 %). 3. The AAQOL outcome not reported (specified in Prescribing Information). 4. Vitals not reported, unsure whether they were reported (although it may be expected they were in a pivotal trial).
Other bias	Low risk	None found.
Psychiatric comorbidity (External validity)	High risk	1. "Having a primary diagnosis of schizophrenia, schizoaffective disorder, primary affective disorder, schizotypal personality, major depression, bipolar disorder, generalized anxiety, borderline personality disorder, antisocial personality or another unstable psychiatric condition requiring treatment, as assessed by the structured interview conducted at Visit 1" (CT.gov).
Responder selection (External validity)	High risk	1. "Known to be non-responsive to methylphenidate treatment. Non-response is defined as methylphenidate use at various doses for a phase of at least four weeks at each dose with little or no clinical benefit" (CT.gov).
Withdrawal effects (External validity)	High risk	1. "Subjects who meet eligibility requirements will undergo ADHD medication washout, if applicable" (CT.gov).

Asherson 2016

Study characteristics	
Methods	**Trial ID(s)**: 2015-004271-78 (EUCTR), ISRCTN16827947, CIAOII. **Trial registry entry**: https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-004271-78/GB. **Sponsor**: King's College, London.

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Asherson 2016 *(Continued)*

	Funding/industry involvement: NIHR EME grant. **Country**: United Kingdom. **No. sites**: 3 sites. **Start - completion**: May 2016 - Jul 2019. **Duration**: 8 weeks. **Sample size**: Estimated 160 participants.
Participants	*Information on exclusion criteria related to psychiatric comorbidity is listed in the risk of bias table.* **ADHD diagnostic system**: DSM V. **Concomitant substance abuse diagnosis**: No. **Mean age (range)**: Range 16 to 25 years. **Males** (%): 100. **Other trial characteristics**: Prison inmates only.
Interventions	**Trial arms**: 1. OROS methylphenidate 2. Placebo **Type of methylphenidate**: OROS methylphenidate. **Dosage range**: 18 mg to 72 mg. **Fixed or titrated**: Titrated. **Administrations per day**: 1 or 2. **Co-intervention(s)**: Not described.
Outcomes	*Relevant outcomes are listed here.* Trial is unpublished and we did not include any data for this review.
Notes	**Declared conflicts of interest**: No publication available, information from EUCTR and ISRCTN only.

Methacan 2017

Study characteristics	
Methods	**Trial ID(s)**: 2017-000386-77 (EUCTR), NCT03481959, P140313 (protocol), METHACAN (trial name). **Trial registry entry**: https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-000386-77/FR, https://clinicaltrials.gov/ct2/show/NCT03481959. **Sponsor**: Assistance Publique - Hopitaux de Paris **Funding/industry involvement**: None **Setting**: France. **No. sites**: 2 sites. **Start - completion**: Not described. **Duration**: 12 weeks. **Sample size**: No data.

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Methacan 2017 *(Continued)*

Participants	*Information on exclusion criteria related to psychiatric comorbidity is listed in the risk of bias table.* **ADHD diagnostic system**: DSM V. **Concomitant substance abuse diagnosis**: Cannabis dependence (not described if DSM or ICD) **Mean age (range)**: Range 12 - 25 years. **Males** (%): No data.
Interventions	**Trial arms**: 1. Ritalin LA 2. Placebo **Type of methylphenidate**: Long acting methylphenidate. **Dosage range**: 10 mg to 30 mg. **Fixed or titrated**: Not described. **Administrations per day**: Not described. **Co-intervention(s)**: Not described.
Outcomes	*Relevant outcomes are listed here.* The trial is ongoing
Notes	**Declared conflicts of interest**: No publication available, information from EUCTR only.

DATA AND ANALYSES

Comparison 1. Extended-release methylphenidate versus placebo: benefits (short term)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Functional outcome: Days missed at work/school/training	2	409	Mean Difference (IV, Random, 95% CI)	-0.15 [-2.11, 1.81]
1.2 ADHD symptoms (self rated)	16	3424	Std. Mean Difference (IV, Random, 95% CI)	-0.38 [-0.45, -0.31]
1.3 ADHD symptoms (self rated) [subgroup mean diff]	16		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.3.1 DSM-IV total ADHD (18 items, 0-54 points)	7	1189	Mean Difference (IV, Random, 95% CI)	-3.05 [-4.34, -1.76]
1.3.2 ASRS (18 items, 0-72 points)	2	953	Mean Difference (IV, Random, 95% CI)	-6.25 [-8.25, -4.25]
1.3.3 CAARS: Short version (26 items, 0-78 points)	4	1076	Mean Difference (IV, Random, 95% CI)	-5.93 [-7.73, -4.12]
1.3.4 CAARS: Long version (66 items, 0-90 points)	1	162	Mean Difference (IV, Random, 95% CI)	-28.40 [-48.28, -8.52]

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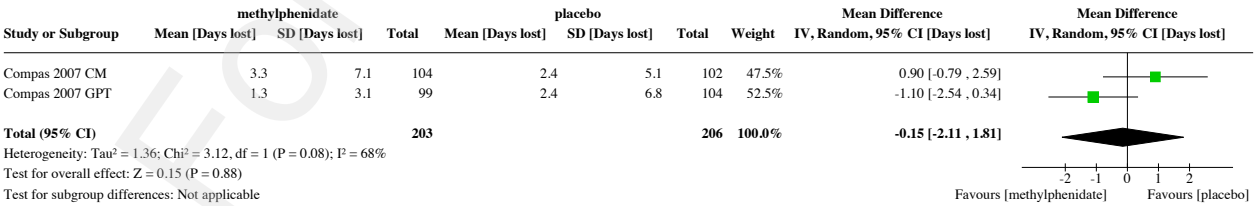
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3.5 CAARS: Unspecified subscale	2	44	Mean Difference (IV, Random, 95% CI)	-8.23 [-17.79, 1.32]
1.4 Quality of life (self rated)	6	1513	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.22, -0.01]
1.5 Quality of life (self rated) [subgroup mean difference]	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.5.1 Q-LES-QSF (14-70 points)	5	1234	Mean Difference (IV, Random, 95% CI)	-0.93 [-2.17, 0.31]
1.5.2 AIM-A total score	1	279	Mean Difference (IV, Random, 95% CI)	-0.50 [-0.99, -0.00]
1.7 ADHD symptoms (investigator rated)	20	4213	Std. Mean Difference (IV, Random, 95% CI)	-0.43 [-0.51, -0.35]
1.8 ADHD symptoms (investigator rated) [subgroup mean diff]	20		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.8.1 DSM-IV Total ADHD (18 items, 0-54 points)	13	3151	Mean Difference (IV, Random, 95% CI)	-5.35 [-6.73, -3.97]
1.8.2 DSM-V Total ADHD (18 items, 0-54 points)	1	375	Mean Difference (IV, Random, 95% CI)	-4.38 [-7.37, -1.39]
1.8.3 WRAADDS (28 items, 0-56 points)	2	521	Mean Difference (IV, Random, 95% CI)	-6.06 [-8.48, -3.63]
1.8.4 CGI (range 0-7)	2	36	Mean Difference (IV, Random, 95% CI)	0.09 [-0.67, 0.86]
1.8.5 TAADS (7 items, 0-28 points)	1	106	Mean Difference (IV, Random, 95% CI)	-3.50 [-7.85, 0.85]
1.8.6 CAARS: Unspecified scale	1	24	Mean Difference (IV, Random, 95% CI)	0.10 [-10.21, 10.41]
1.9 ADHD symptoms (peer rated)	2	630	Std. Mean Difference (IV, Random, 95% CI)	-0.39 [-0.57, -0.22]

Analysis 1.1. Comparison 1: Extended-release methylphenidate versus placebo: benefits (short term), Outcome 1: Functional outcome: Days missed at work/school/training



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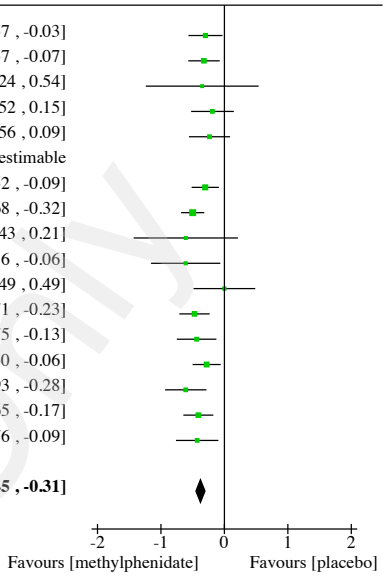
Analysis 1.2. Comparison 1: Extended-release methylphenidate versus placebo: benefits (short term), Outcome 2: ADHD symptoms (self rated)

Study or Subgroup	methylphenidate Mean	SD	Total	placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Adler 2006	-12.7	14.6443	102	-8.3	14.6916	115	7.1%	-0.30 [-0.57 , -0.03]
Casas 2008	35.4484	15.3148	182	40.3	14.5	97	8.3%	-0.32 [-0.57 , -0.07]
Chronis-Tuscano 2004	54.44	12.82	9	60.27	18.07	11	0.6%	-0.35 [-1.24 , 0.54]
Compas 2007 CM	19.9	9.7	83	21.8	10.5	58	4.5%	-0.19 [-0.52 , 0.15]
Compas 2007 GPT	19.8	8.7	79	21.9	9.1	69	4.9%	-0.24 [-0.56 , 0.09]
Ginsberg 2007	36.8	12.0986	15	54.7	9.0288	15		Not estimable
Goodman 2009	32.6	16.04	167	37.5	16.33	171	11.1%	-0.30 [-0.52 , -0.09]
Huss 2010	37.9728	13.9919	456	44.9	13.41	159	15.4%	-0.50 [-0.68 , -0.32]
Konstenius 2006	-19.1	13.2	12	-8.5	19.8	12	0.8%	-0.61 [-1.43 , 0.21]
Konstenius 2007	23.8	10	27	30	10	27	1.7%	-0.61 [-1.16 , -0.06]
Levin 1998a	22	10	32	22	10	33	2.2%	0.00 [-0.49 , 0.49]
Medori 2005	-12.0196	13.7233	280	-5.8	11.3	91	9.0%	-0.47 [-0.71 , -0.23]
Retz 2008	-41.5	64.5	84	-13.1	64.5	78	5.3%	-0.44 [-0.75 , -0.13]
Rösler 2004	20.1	9.28	241	22.7	9.28	118	10.5%	-0.28 [-0.50 , -0.06]
Spencer 2003	35	15.3	160	44.4	15.6	49	4.8%	-0.61 [-0.93 , -0.28]
Takahashi 2011	-10.7	9.85	141	-6.6	10.06	140	9.2%	-0.41 [-0.65 , -0.17]
Weisler 2009	-7.3	16.9385	68	0	16.9	73	4.6%	-0.43 [-0.76 , -0.09]
Total (95% CI)			**2123**			**1301**	**100.0%**	**-0.38 [-0.45 , -0.31]**

Heterogeneity: Tau² = 0.00; Chi² = 11.61, df = 15 (P = 0.71); I² = 0%
Test for overall effect: Z = 10.33 (P < 0.00001)
Test for subgroup differences: Not applicable



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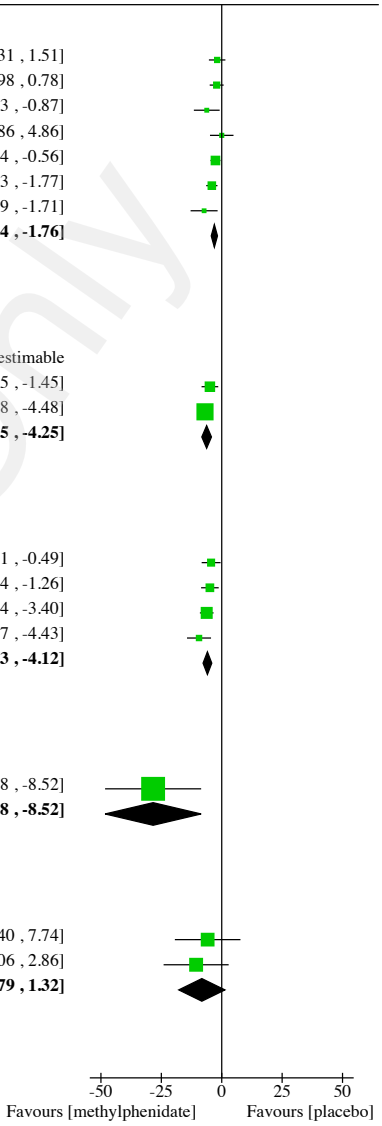
Analysis 1.3. Comparison 1: Extended-release methylphenidate versus placebo: benefits (short term), Outcome 3: ADHD symptoms (self rated) [subgroup mean diff]

Study or Subgroup	methylphenidate Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.3.1 DSM-IV total ADHD (18 items, 0-54 points)								
Compas 2007 CM	19.9	9.7	83	21.8	10.5	58	12.6%	-1.90 [-5.31 , 1.51]
Compas 2007 GPT	19.8	8.7	79	21.9	9.1	69	17.0%	-2.10 [-4.98 , 0.78]
Konstenius 2007	23.8	10	27	30	10	27	5.6%	-6.20 [-11.53 , -0.87]
Levin 1998a	22	10	32	22	10	33	6.6%	0.00 [-4.86 , 4.86]
Rösler 2004	20.1	9.28	241	22.7	9.28	118	29.2%	-2.60 [-4.64 , -0.56]
Takahashi 2011	-10.7	9.85	141	-6.6	10.06	140	24.0%	-4.10 [-6.43 , -1.77]
Weisler 2009	-7.3	16.9385	68	0	16.9	73	5.1%	-7.30 [-12.89 , -1.71]
Subtotal (95% CI)			**671**			**518**	**100.0%**	**-3.05 [-4.34 , -1.76]**
Heterogeneity: Tau² = 0.40; Chi² = 6.89, df = 6 (P = 0.33); I² = 13%								
Test for overall effect: Z = 4.63 (P < 0.00001)								
1.3.2 ASRS (18 items, 0-72 points)								
Ginsberg 2007	36.8	12.0986	15	54.7	9.0288	15		Not estimable
Goodman 2009	32.6	16.04	167	37.5	16.33	171	33.5%	-4.90 [-8.35 , -1.45]
Huss 2010	37.9728	13.9919	456	44.9	13.41	159	66.5%	-6.93 [-9.38 , -4.48]
Subtotal (95% CI)			**623**			**330**	**100.0%**	**-6.25 [-8.25 , -4.25]**
Heterogeneity: Tau² = 0.00; Chi² = 0.88, df = 1 (P = 0.35); I² = 0%								
Test for overall effect: Z = 6.13 (P < 0.00001)								
1.3.3 CAARS: Short version (26 items, 0-78 points)								
Adler 2006	-12.7	14.6443	102	-8.3	14.6916	115	21.3%	-4.40 [-8.31 , -0.49]
Casas 2008	35.4	15.3	182	40.3	14.5	97	24.6%	-4.90 [-8.54 , -1.26]
Medori 2005	-12.0196	13.7233	280	-5.8	11.3	91	40.9%	-6.22 [-9.04 , -3.40]
Spencer 2003	35	15.3	160	44.4	15.6	49	13.2%	-9.40 [-14.37 , -4.43]
Subtotal (95% CI)			**724**			**352**	**100.0%**	**-5.93 [-7.73 , -4.12]**
Heterogeneity: Tau² = 0.00; Chi² = 2.81, df = 3 (P = 0.42); I² = 0%								
Test for overall effect: Z = 6.43 (P < 0.00001)								
1.3.4 CAARS: Long version (66 items, 0-90 points)								
Retz 2008	-41.5	64.5	84	-13.1	64.5	78	100.0%	-28.40 [-48.28 , -8.52]
Subtotal (95% CI)			**84**			**78**	**100.0%**	**-28.40 [-48.28 , -8.52]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.80 (P = 0.005)								
1.3.5 CAARS: Unspecified subscale								
Chronis-Tuscano 2004	54.44	12.82	9	60.27	18.07	11	49.6%	-5.83 [-19.40 , 7.74]
Konstenius 2006	-19.1	13.2	12	-8.5	19.8	12	50.4%	-10.60 [-24.06 , 2.86]
Subtotal (95% CI)			**21**			**23**	**100.0%**	**-8.23 [-17.79 , 1.32]**
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.62); I² = 0%								
Test for overall effect: Z = 1.69 (P = 0.09)								
Test for subgroup differences: Chi² = 16.27, df = 4 (P = 0.003), I² = 75.4%								



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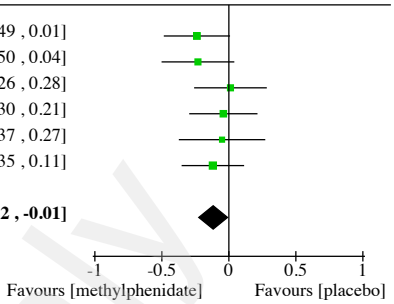
Analysis 1.4. Comparison 1: Extended-release methylphenidate versus placebo: benefits (short term), Outcome 4: Quality of life (self rated)

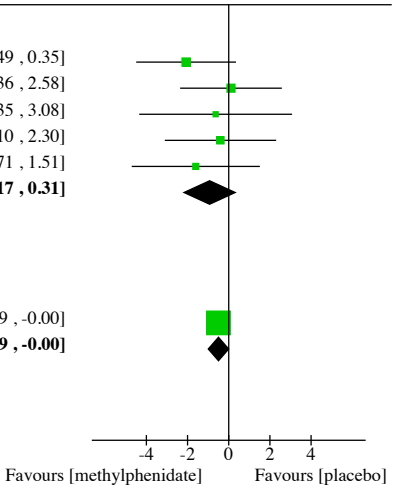
Study or Subgroup	methylphenidate Mean	SD	Total	placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Casas 2008	-0.8978	2.1583	182	-0.4	1.93	97	18.8%	-0.24 [-0.49 , 0.01]
Compas 2007 CM	-48.61	8.4523	107	-46.54	9.4147	103	15.6%	-0.23 [-0.50 , 0.04]
Compas 2007 GPT	-47.21	8.596	103	-47.32	9.606	106	15.6%	0.01 [-0.26 , 0.28]
Medori 2005	-5.6341	15.7824	246	-5	14.17	78	17.7%	-0.04 [-0.30 , 0.21]
Spencer 2003	-51.3	7.6	160	-50.9	8.6	48	11.1%	-0.05 [-0.37 , 0.27]
Takahashi 2011	-2.4	14	143	-0.8	12.69	140	21.1%	-0.12 [-0.35 , 0.11]
Total (95% CI)			**941**			**572**	**100.0%**	**-0.12 [-0.22 , -0.01]**

Heterogeneity: Tau² = 0.00; Chi² = 2.98, df = 5 (P = 0.70); I² = 0%
Test for overall effect: Z = 2.14 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Extended-release methylphenidate versus placebo: benefits (short term), Outcome 5: Quality of life (self rated) [subgroup mean difference]

Study or Subgroup	methylphenidate Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.5.1 Q-LES-QSF (14-70 points)								
Compas 2007 CM	-48.61	8.4523	107	-46.54	9.4147	103	26.3%	-2.07 [-4.49 , 0.35]
Compas 2007 GPT	-47.21	8.596	103	-47.32	9.606	106	25.3%	0.11 [-2.36 , 2.58]
Medori 2005	-5.6341	15.7824	246	-5	14.17	78	11.2%	-0.63 [-4.35 , 3.08]
Spencer 2003	-51.3	7.6	160	-50.9	8.6	48	21.2%	-0.40 [-3.10 , 2.30]
Takahashi 2011	-2.4	14	143	-0.8	12.69	140	16.0%	-1.60 [-4.71 , 1.51]
Subtotal (95% CI)			**759**			**475**	**100.0%**	**-0.93 [-2.17 , 0.31]**
Heterogeneity: Tau² = 0.00; Chi² = 1.88, df = 4 (P = 0.76); I² = 0%								
Test for overall effect: Z = 1.46 (P = 0.14)								
1.5.2 AIM-A total score								
Casas 2008	-0.8978	2.1583	182	-0.4	1.93	97	100.0%	-0.50 [-0.99 , -0.00]
Subtotal (95% CI)			**182**			**97**	**100.0%**	**-0.50 [-0.99 , -0.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.97 (P = 0.05)								
Test for subgroup differences: Chi² = 0.40, df = 1 (P = 0.53), I² = 0%								



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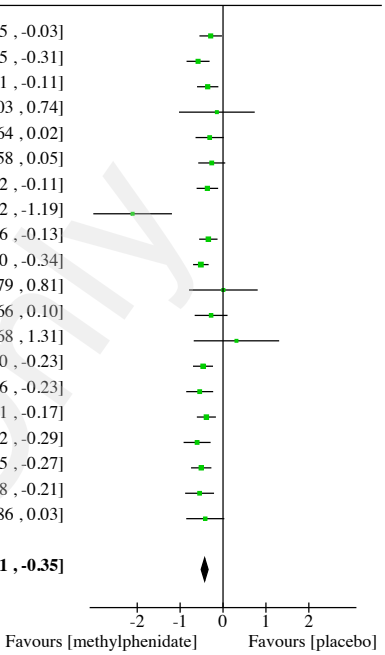
Analysis 1.7. Comparison 1: Extended-release methylphenidate versus placebo: benefits (short term), Outcome 7: ADHD symptoms (investigator rated)

Study or Subgroup	methylphenidate Mean	SD	Total	placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Adler 2006	27.6	13.27	110	31.3	12.38	116	6.4%	-0.29 [-0.55 , -0.03]
Biederman 2003	13.8	11.0667	109	20.4	11.5312	114	6.2%	-0.58 [-0.85 , -0.31]
Casas 2008	22.2923	10.6376	182	26.1	10.6	97	6.8%	-0.36 [-0.61 , -0.11]
Chronis-Tuscano 2004	3.11	1.17	9	3.3	1.34	11	0.8%	-0.14 [-1.03 , 0.74]
Compas 2007 CM	19	9.1	85	21.9	9.5	62	4.6%	-0.31 [-0.64 , 0.02]
Compas 2007 GPT	18.8	7.5	82	20.9	8.4	75	4.9%	-0.26 [-0.58 , 0.05]
Foquest 2014	21.7236	11.9669	297	26.1	11.99	78	6.8%	-0.36 [-0.62 , -0.11]
Ginsberg 2007	20.4	10.1123	15	38.1	5.5979	15	0.7%	-2.11 [-3.02 , -1.19]
Goodman 2009	20.7	12.76	169	25.2	13.47	172	8.2%	-0.34 [-0.56 , -0.13]
Huss 2010	23.4013	11.8312	471	29.5	11.64	161	9.9%	-0.52 [-0.70 , -0.34]
Konstenius 2006	-3.9	11.9	12	-4	13.8	12	1.0%	0.01 [-0.79 , 0.81]
Levin 1998b	10.1	9.4641	53	13.3	13.1042	53	3.6%	-0.28 [-0.66 , 0.10]
Levin 2001	4.5	1.11	9	4.14	1.0583	7	0.6%	0.31 [-0.68 , 1.31]
Medori 2005	24.5749	10.7903	299	29.6	10.6	95	7.4%	-0.47 [-0.70 , -0.23]
Retz 2008	32.5	12.9024	84	39.2	11.5317	78	4.9%	-0.54 [-0.86 , -0.23]
Rösler 2004	26	14.4	241	31.6	14.4	118	7.9%	-0.39 [-0.61 , -0.17]
Spencer 2003	22.2164	11.6839	165	29.6	13.6	53	4.9%	-0.60 [-0.92 , -0.29]
Takahashi 2011	-12.5	9.0739	143	-7.9	8.9766	140	7.3%	-0.51 [-0.75 , -0.27]
Weisler 2009	-15.7	13.39	68	-8.8	11.74	73	4.4%	-0.55 [-0.88 , -0.21]
Winhusen 2005	16.4	12.2	38	24.2	23	42	2.8%	-0.41 [-0.86 , 0.03]
Total (95% CI)			**2641**			**1572**	**100.0%**	**-0.43 [-0.51 , -0.35]**

Heterogeneity: Tau² = 0.01; Chi² = 26.04, df = 19 (P = 0.13); I² = 27%
Test for overall effect: Z = 10.47 (P < 0.00001)
Test for subgroup differences: Not applicable



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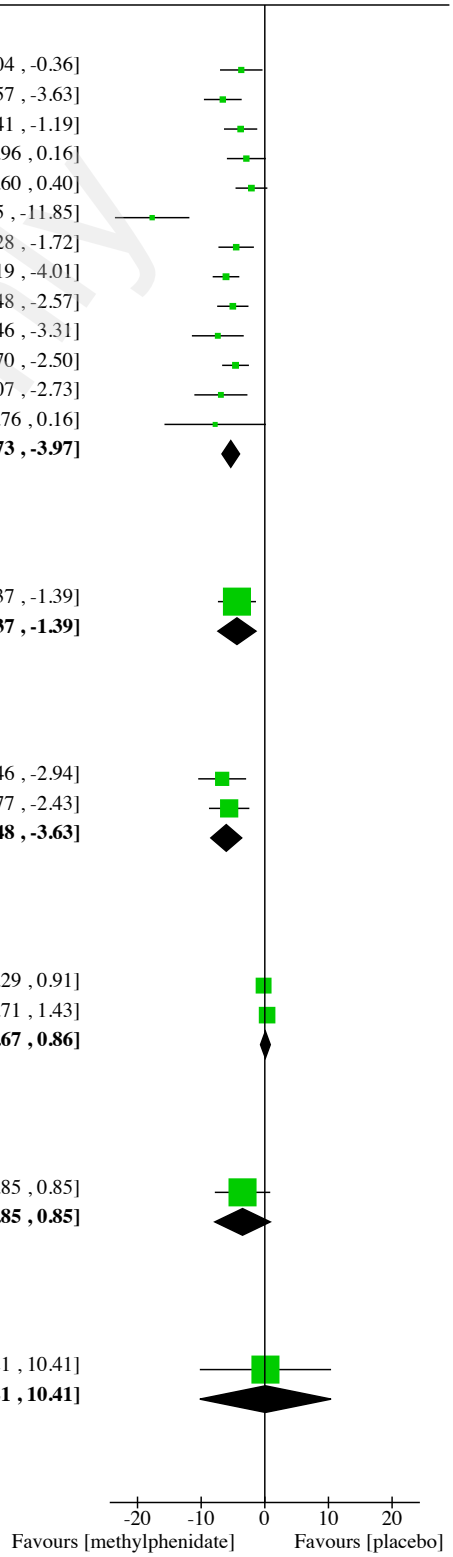
Analysis 1.8. Comparison 1: Extended-release methylphenidate versus placebo: benefits (short term), Outcome 8: ADHD symptoms (investigator rated) [subgroup mean diff]

Study or Subgroup	methylphenidate Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.8.1 DSM-IV Total ADHD (18 items, 0-54 points)								
Adler 2006	27.6	13.17	110	31.3	12.38	116	7.6%	-3.70 [-7.04 , -0.36]
Biederman 2003	13.8	11.0667	109	20.4	11.5312	114	8.3%	-6.60 [-9.57 , -3.63]
Casas 2008	22.3	10.6	182	26.1	10.6	97	9.1%	-3.80 [-6.41 , -1.19]
Compas 2007 CM	19	9.1	85	21.9	9.5	62	8.1%	-2.90 [-5.96 , 0.16]
Compas 2007 GPT	18.8	7.5	82	20.9	8.4	75	9.4%	-2.10 [-4.60 , 0.40]
Ginsberg 2007	20.4	10.1123	15	38.1	5.5979	15	4.0%	-17.70 [-23.55 , -11.85]
Goodman 2009	20.7	12.76	169	25.2	13.47	172	8.7%	-4.50 [-7.28 , -1.72]
Huss 2010	23.4013	11.8312	471	29.5	11.64	161	10.3%	-6.10 [-8.19 , -4.01]
Medori 2005	24.5749	10.7903	299	29.6	10.6	95	9.5%	-5.03 [-7.48 , -2.57]
Spencer 2003	22.2164	11.6839	165	29.6	13.6	53	6.2%	-7.38 [-11.46 , -3.31]
Takahashi 2011	-12.5	9.0739	143	-7.9	8.9766	140	10.3%	-4.60 [-6.70 , -2.50]
Weisler 2009	-15.7	13.39	68	-8.8	11.74	73	6.1%	-6.90 [-11.07 , -2.73]
Winhusen 2005	16.4	12.2	38	24.2	23	42	2.5%	-7.80 [-15.76 , 0.16]
Subtotal (95% CI)			**1936**			**1215**	**100.0%**	**-5.35 [-6.73 , -3.97]**
Heterogeneity: Tau² = 3.69; Chi² = 31.52, df = 12 (P = 0.002); I² = 62%								
Test for overall effect: Z = 7.58 (P < 0.00001)								
1.8.2 DSM-V Total ADHD (18 items, 0-54 points)								
Foquest 2014	21.7236	11.9669	297	26.1	11.99	78	100.0%	-4.38 [-7.37 , -1.39]
Subtotal (95% CI)			**297**			**78**	**100.0%**	**-4.38 [-7.37 , -1.39]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.87 (P = 0.004)								
1.8.3 WRAADDS (28 items, 0-56 points)								
Retz 2008	32.5	12.9024	84	39.2	11.5317	78	41.5%	-6.70 [-10.46 , -2.94]
Rösler 2004	26	14.4	241	31.6	14.4	118	58.5%	-5.60 [-8.77 , -2.43]
Subtotal (95% CI)			**325**			**196**	**100.0%**	**-6.06 [-8.48 , -3.63]**
Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.66); I² = 0%								
Test for overall effect: Z = 4.90 (P < 0.00001)								
1.8.4 CGI (range 0-7)								
Chronis-Tuscano 2004	3.11	1.17	9	3.3	1.34	11	48.5%	-0.19 [-1.29 , 0.91]
Levin 2001	4.5	1.11	9	4.14	1.0583	7	51.5%	0.36 [-0.71 , 1.43]
Subtotal (95% CI)			**18**			**18**	**100.0%**	**0.09 [-0.67 , 0.86]**
Heterogeneity: Tau² = 0.00; Chi² = 0.49, df = 1 (P = 0.48); I² = 0%								
Test for overall effect: Z = 0.24 (P = 0.81)								
1.8.5 TAADS (7 items, 0-28 points)								
Levin 1998b	10	9.4641	53	13.5	13.1042	53	100.0%	-3.50 [-7.85 , 0.85]
Subtotal (95% CI)			**53**			**53**	**100.0%**	**-3.50 [-7.85 , 0.85]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.58 (P = 0.11)								
1.8.6 CAARS: Unspecified scale								
Konstenius 2006	-3.9	11.9	12	-4	13.8	12	100.0%	0.10 [-10.21 , 10.41]
Subtotal (95% CI)			**12**			**12**	**100.0%**	**0.10 [-10.21 , 10.41]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.02 (P = 0.98)								



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Analysis 1.9. Comparison 1: Extended-release methylphenidate versus placebo: benefits (short term), Outcome 9: ADHD symptoms (peer rated)

Comparison 2. Extended-release methylphenidate versus placebo: harms (short term)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Serious adverse events	14	4078	Risk Ratio (IV, Random, 95% CI)	1.43 [0.85, 2.43]
2.2 Cardiovascular: Systolic blood pressure	9	2031	Mean Difference (IV, Random, 95% CI)	0.44 [-0.67, 1.54]
2.3 Cardiovascular: Diastolic blood pressure	9	2031	Mean Difference (IV, Random, 95% CI)	1.08 [-0.27, 2.43]
2.4 Cardiovascular: Pulse (beats per minute)	10	2314	Mean Difference (IV, Random, 95% CI)	4.26 [2.27, 6.25]
2.5 Weight (Change in kilo grams)	8	1720	Mean Difference (IV, Random, 95% CI)	-1.83 [-2.53, -1.14]
2.6 Dropout (overall)	22	4769	Risk Ratio (IV, Random, 95% CI)	1.01 [0.84, 1.21]
2.7 Dropout (due to adverse events)	15	3963	Risk Ratio (IV, Random, 95% CI)	2.36 [1.62, 3.43]
2.8 Adverse events (proportion experiencing any adverse event)	14	4214	Risk Ratio (IV, Random, 95% CI)	1.27 [1.19, 1.37]
2.10 Psychiatric adverse events (proportion of participants)	6	2482	Risk Ratio (IV, Random, 95% CI)	1.99 [1.54, 2.58]
2.11 Adverse event: Decreased appetite	16	4491	Risk Ratio (IV, Random, 95% CI)	4.08 [3.34, 4.98]
2.12 Adverse event: Dry mouth	16	4491	Risk Ratio (IV, Random, 95% CI)	3.36 [2.61, 4.34]
2.13 Adverse event: Headache	16	4238	Risk Ratio (IV, Random, 95% CI)	1.35 [1.18, 1.54]
2.15 Adverse event: Palpitations	15	4212	Risk Ratio (IV, Random, 95% CI)	3.71 [2.52, 5.46]
2.16 Adverse event: Insomnia	16	4435	Risk Ratio (IV, Random, 95% CI)	1.97 [1.51, 2.57]
2.17 Adverse event: Sexual dysfunction	7	3057	Risk Ratio (IV, Random, 95% CI)	2.66 [1.31, 5.39]

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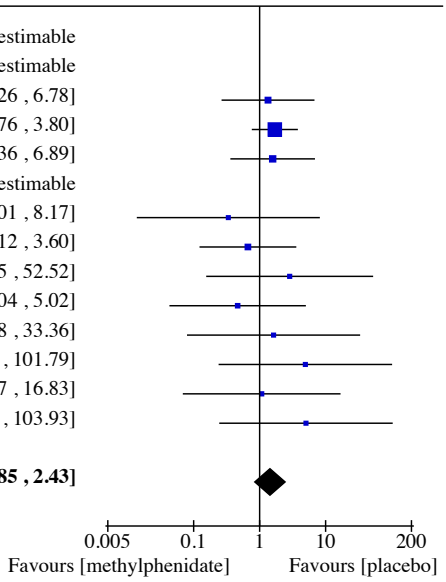
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.18 Adverse event: Anxiety	13	3829	Risk Ratio (IV, Random, 95% CI)	2.23 [1.40, 3.57]
2.19 Adverse event: Depression	7	2791	Risk Ratio (IV, Random, 95% CI)	1.47 [0.87, 2.49]
2.20 Adverse event: Irritability	11	3377	Risk Ratio (IV, Random, 95% CI)	1.39 [1.00, 1.93]
2.21 Adverse event: Feeling jittery	7	2254	Risk Ratio (IV, Random, 95% CI)	5.52 [2.77, 10.99]
2.22 Adverse event: Agitation	8	3166	Risk Ratio (IV, Random, 95% CI)	2.16 [1.25, 3.71]
2.23 Adverse event: aggression	2	1319	Risk Ratio (IV, Random, 95% CI)	2.10 [1.32, 3.33]

Analysis 2.1. Comparison 2: Extended-release methylphenidate versus placebo: harms (short term), Outcome 1: Serious adverse events

Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Adler 2006	0	110	0	116		Not estimable
Biederman 2003	0	109	0	114		Not estimable
Casas 2008	5	181	2	97	10.6%	1.34 [0.26 , 6.78]
Compas 2007 CM	15	205	9	209	43.1%	1.70 [0.76 , 3.80]
Foquest 2014	12	297	2	78	12.8%	1.58 [0.36 , 6.89]
Ginsberg 2007	0	15	0	15		Not estimable
Goodman 2009	0	174	1	175	2.7%	0.34 [0.01 , 8.17]
Huss 2010	4	542	2	180	9.8%	0.66 [0.12 , 3.60]
Medori 2005	4	305	0	96	3.3%	2.85 [0.15 , 52.52]
Retz 2008	1	84	2	78	4.9%	0.46 [0.04 , 5.02]
Spencer 2003	2	165	0	53	3.1%	1.63 [0.08 , 33.36]
Takahashi 2011	2	143	0	141	3.0%	4.93 [0.24 , 101.79]
Weisler 2009	1	68	1	73	3.7%	1.07 [0.07 , 16.83]
Winhusen 2005	2	127	0	128	3.0%	5.04 [0.24 , 103.93]
Total (95% CI)		**2525**		**1553**	**100.0%**	**1.43 [0.85 , 2.43]**
Total events:	48		19			

Heterogeneity: Tau² = 0.00; Chi² = 4.21, df = 10 (P = 0.94); I² = 0%
Test for overall effect: Z = 1.34 (P = 0.18)
Test for subgroup differences: Not applicable



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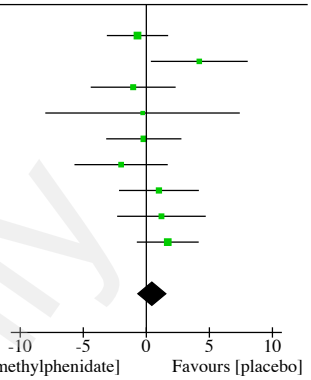
Analysis 2.2. Comparison 2: Extended-release methylphenidate versus placebo: harms (short term), Outcome 2: Cardiovascular: Systolic blood pressure

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Adler 2006	-1.2	8.92	110	-0.5	9.72	116	18.8%	-0.70 [-3.13 , 1.73]
Biederman 2003	122.6	11.9	67	118.4	11.3	74	8.0%	4.20 [0.36 , 8.04]
Casas 2008	121.3575	14.285	181	122.4	13.3	97	10.3%	-1.04 [-4.41 , 2.32]
Ginsberg 2007	135.6	11.5569	15	135.9	9.9317	15	2.0%	-0.30 [-8.01 , 7.41]
Medori 2005	0.9	13	305	1.1	13	96	12.9%	-0.20 [-3.18 , 2.78]
Retz 2008	123	12	84	125	12	78	8.6%	-2.00 [-5.70 , 1.70]
Rösler 2004	124	13	241	123	15	118	11.5%	1.00 [-2.17 , 4.17]
Spencer 2003	-0.5	11.5	165	-1.7	11.3	53	9.5%	1.20 [-2.31 , 4.71]
Winhusen 2005	1.8	10	107	0.1	8.3	109	18.5%	1.70 [-0.75 , 4.15]
Total (95% CI)			**1275**			**756**	**100.0%**	**0.44 [-0.67 , 1.54]**

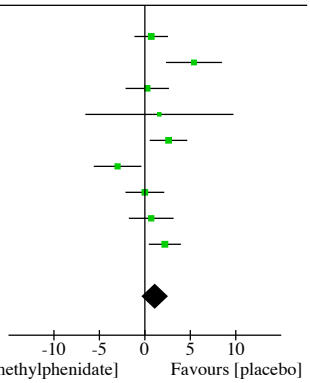
Heterogeneity: Tau² = 0.16; Chi² = 8.47, df = 8 (P = 0.39); I² = 6%
Test for overall effect: Z = 0.77 (P = 0.44)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Extended-release methylphenidate versus placebo: harms (short term), Outcome 3: Cardiovascular: Diastolic blood pressure

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Adler 2006	1.1	6.72	110	0.4	7.43	116	13.8%	0.70 [-1.15 , 2.55]
Biederman 2003	72.8	9.3	67	67.4	9.3	74	9.5%	5.40 [2.33 , 8.47]
Casas 2008	74.5641	9.4123	181	74.3	9.8	97	11.8%	0.26 [-2.12 , 2.65]
Ginsberg 2007	74.4	11.0152	15	72.8	11.7375	15	2.4%	1.60 [-6.55 , 9.75]
Medori 2005	0.8	9	305	-1.8	9	96	13.0%	2.60 [0.54 , 4.66]
Retz 2008	80	9	84	83	8	78	11.0%	-3.00 [-5.62 , -0.38]
Rösler 2004	78	9	241	78	10	118	12.7%	0.00 [-2.13 , 2.13]
Spencer 2003	1	8.4	165	0.3	7.8	53	11.5%	0.70 [-1.76 , 3.16]
Winhusen 2005	1.4	7	107	-0.8	6.2	109	14.2%	2.20 [0.44 , 3.96]
Total (95% CI)			**1275**			**756**	**100.0%**	**1.08 [-0.27 , 2.43]**

Heterogeneity: Tau² = 2.56; Chi² = 22.25, df = 8 (P = 0.004); I² = 64%
Test for overall effect: Z = 1.56 (P = 0.12)
Test for subgroup differences: Not applicable



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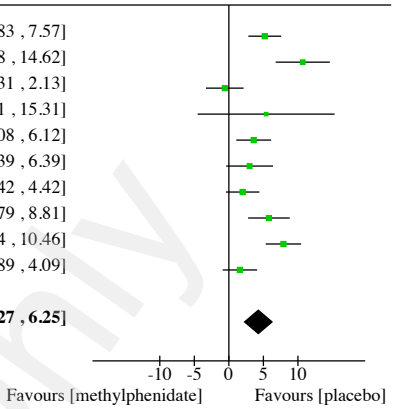
Analysis 2.4. Comparison 2: Extended-release methylphenidate versus placebo: harms (short term), Outcome 4: Cardiovascular: Pulse (beats per minute)

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Adler 2006	3.6	9.78	110	-1.6	8.33	116	11.5%	5.20 [2.83 , 7.57]
Biederman 2003	82.9	12.5	67	72.2	11.1	74	9.0%	10.70 [6.78 , 14.62]
Casas 2008	69.3116	11.1004	181	69.9	11	97	10.9%	-0.59 [-3.31 , 2.13]
Ginsberg 2007	70.9	12.8209	15	65.5	14.8073	15	3.1%	5.40 [-4.51 , 15.31]
Medori 2005	6.3	11	305	2.7	11	96	11.3%	3.60 [1.08 , 6.12]
Retz 2008	76	11	84	73	11	78	9.8%	3.00 [-0.39 , 6.39]
Rösler 2004	76	11	241	74	11	118	11.4%	2.00 [-0.42 , 4.42]
Spencer 2003	4.4	11	165	-1.4	9.3	53	10.5%	5.80 [2.79 , 8.81]
Takahashi 2011	9.2	11	143	1.3	11	140	11.2%	7.90 [5.34 , 10.46]
Winhusen 2005	2.2	10.2	107	0.6	8.4	109	11.3%	1.60 [-0.89 , 4.09]
Total (95% CI)			**1418**			**896**	**100.0%**	**4.26 [2.27 , 6.25]**

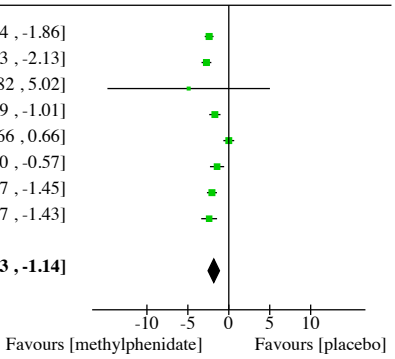
Heterogeneity: Tau² = 7.48; Chi² = 40.07, df = 9 (P < 0.00001); I² = 78%
Test for overall effect: Z = 4.20 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: Extended-release methylphenidate versus placebo: harms (short term), Outcome 5: Weight (Change in kilo grams)

Study or Subgroup	Methylphenidate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Adler 2006	-2.2	2.33	110	0.2	1.74	116	15.2%	-2.40 [-2.94 , -1.86]
Biederman 2003	-2.7	1.9	67	0.03	1.7	74	14.9%	-2.73 [-3.33 , -2.13]
Ginsberg 2007	85.9	12.6404	15	90.8	14.9879	15	0.5%	-4.90 [-14.82 , 5.02]
Medori 2005	-1.3	3	305	0.4	3	96	14.3%	-1.70 [-2.39 , -1.01]
Rösler 2004	77	3	241	77	3	118	14.5%	0.00 [-0.66 , 0.66]
Spencer 2003	-1.4327	2.0697	165	0	3	53	13.3%	-1.43 [-2.30 , -0.57]
Weisler 2009	-1.47	1.934	68	0.59	1.748	73	14.8%	-2.06 [-2.67 , -1.45]
Winhusen 2005	-1.4	3.1	102	1	3.9	102	12.6%	-2.40 [-3.37 , -1.43]
Total (95% CI)			**1073**			**647**	**100.0%**	**-1.83 [-2.53 , -1.14]**

Heterogeneity: Tau² = 0.76; Chi² = 45.55, df = 7 (P < 0.00001); I² = 85%
Test for overall effect: Z = 5.16 (P < 0.00001)
Test for subgroup differences: Not applicable



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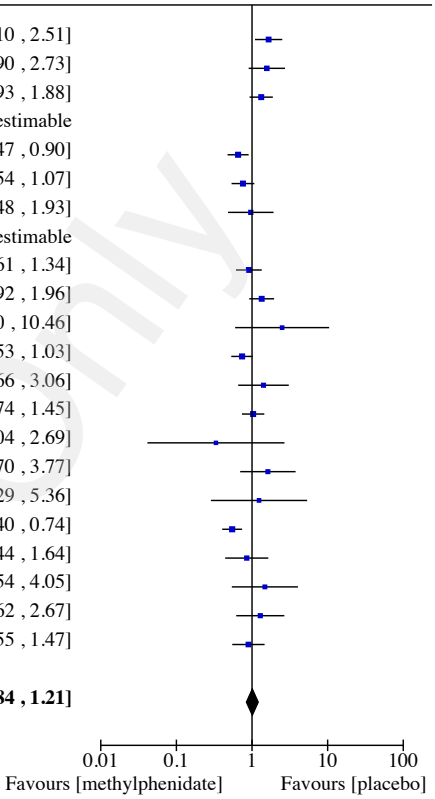
Analysis 2.6. Comparison 2: Extended-release methylphenidate versus placebo: harms (short term), Outcome 6: Dropout (overall)

Study or Subgroup	methylphenidate Events	Total	placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Adler 2006	42	113	26	116	6.5%	1.66 [1.10 , 2.51]
Biederman 2003	26	112	17	115	5.1%	1.57 [0.90 , 2.73]
Casas 2008	72	182	29	97	7.2%	1.32 [0.93 , 1.88]
Chronis-Tuscano 2004	0	9	0	11		Not estimable
Compas 2007 CM	37	110	55	107	7.6%	0.65 [0.47 , 0.90]
Compas 2007 GPT	35	107	47	109	7.3%	0.76 [0.54 , 1.07]
Foquest 2014	33	297	9	78	4.0%	0.96 [0.48 , 1.93]
Ginsberg 2007	0	15	0	15		Not estimable
Goodman 2009	37	178	41	179	6.8%	0.91 [0.61 , 1.34]
Huss 2010	113	544	28	181	6.9%	1.34 [0.92 , 1.96]
Konstenius 2006	5	12	2	12	1.3%	2.50 [0.60 , 10.46]
Konstenius 2007	17	27	23	27	7.5%	0.74 [0.53 , 1.03]
Levin 1998a	11	32	8	33	3.5%	1.42 [0.66 , 3.06]
Levin 1998b	30	53	29	53	7.4%	1.03 [0.74 , 1.45]
Levin 2001	1	10	3	10	0.7%	0.33 [0.04 , 2.69]
Medori 2005	31	306	6	96	3.1%	1.62 [0.70 , 3.77]
Retz 2008	4	84	3	78	1.3%	1.24 [0.29 , 5.36]
Rösler 2004	58	241	52	118	7.8%	0.55 [0.40 , 0.74]
Spencer 2003	27	168	10	53	4.2%	0.85 [0.44 , 1.64]
Takahashi 2011	9	143	6	141	2.4%	1.48 [0.54 , 4.05]
Weisler 2009	13	68	11	74	3.7%	1.29 [0.62 , 2.67]
Winhusen 2005	24	127	27	128	5.7%	0.90 [0.55 , 1.47]
Total (95% CI)		**2938**		**1831**	**100.0%**	**1.01 [0.84 , 1.21]**
Total events:	625		432			

Heterogeneity: Tau² = 0.08; Chi² = 45.81, df = 19 (P = 0.0005); I² = 59%
Test for overall effect: Z = 0.10 (P = 0.92)
Test for subgroup differences: Not applicable



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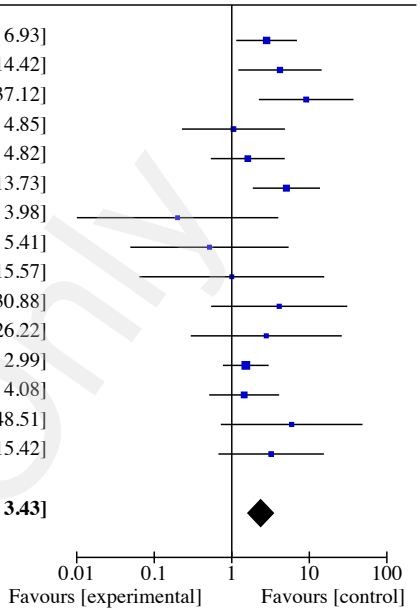
Analysis 2.7. Comparison 2: Extended-release methylphenidate versus placebo: harms (short term), Outcome 7: Dropout (due to adverse events)

Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Adler 2006	16	110	6	116	12.6%	2.81 [1.14 , 6.93]
Biederman 2003	12	109	3	114	7.7%	4.18 [1.21 , 14.42]
Casas 2008	34	181	2	97	6.2%	9.11 [2.24 , 37.12]
Foquest 2014	8	297	2	78	5.3%	1.05 [0.23 , 4.85]
Goodman 2009	8	174	5	175	9.3%	1.61 [0.54 , 4.82]
Huss 2010	61	542	4	180	10.8%	5.06 [1.87 , 13.73]
Konstenius 2007	0	27	2	27	1.5%	0.20 [0.01 , 3.98]
Levin 1998a	1	32	2	33	2.4%	0.52 [0.05 , 5.41]
Levin 1998b	1	53	1	53	1.8%	1.00 [0.06 , 15.57]
Medori 2005	13	305	1	96	3.2%	4.09 [0.54 , 30.88]
Retz 2008	3	84	1	78	2.6%	2.79 [0.30 , 26.22]
Rösler 2004	31	241	10	118	18.3%	1.52 [0.77 , 2.99]
Spencer 2003	18	165	4	53	10.2%	1.45 [0.51 , 4.08]
Takahashi 2011	6	143	1	141	3.0%	5.92 [0.72 , 48.51]
Weisler 2009	6	68	2	73	5.1%	3.22 [0.67 , 15.42]
Total (95% CI)		**2531**		**1432**	**100.0%**	**2.36 [1.62 , 3.43]**
Total events:	218		46			

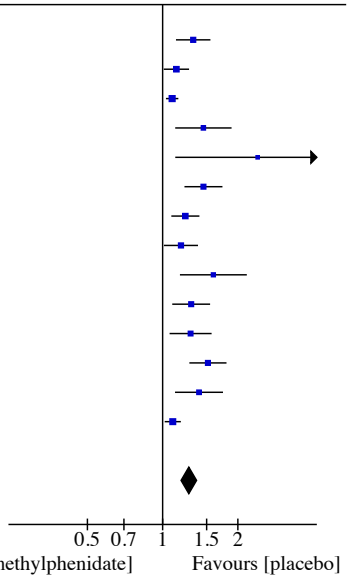
Heterogeneity: Tau² = 0.08; Chi² = 16.57, df = 14 (P = 0.28); I² = 16%
Test for overall effect: Z = 4.46 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.8. Comparison 2: Extended-release methylphenidate versus placebo: harms (short term), Outcome 8: Adverse events (proportion experiencing any adverse event)

Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Adler 2006	93	110	74	116	7.8%	1.33 [1.13 , 1.55]
Casas 2008	161	181	76	97	9.4%	1.14 [1.01 , 1.28]
Compas 2007 CM	197	205	184	209	11.7%	1.09 [1.03 , 1.16]
Foquest 2014	194	297	35	78	4.7%	1.46 [1.12 , 1.89]
Ginsberg 2007	12	15	5	15	0.8%	2.40 [1.12 , 5.13]
Goodman 2009	126	174	87	175	7.2%	1.46 [1.22 , 1.74]
Huss 2010	401	542	108	180	8.9%	1.23 [1.08 , 1.40]
Medori 2005	237	305	63	96	7.8%	1.18 [1.01 , 1.39]
Retz 2008	55	84	32	78	3.8%	1.60 [1.17 , 2.17]
Rösler 2004	178	241	67	118	7.2%	1.30 [1.09 , 1.55]
Spencer 2003	145	165	36	53	6.5%	1.29 [1.07 , 1.57]
Takahashi 2011	117	143	76	141	7.3%	1.52 [1.28 , 1.80]
Weisler 2009	56	68	43	73	5.7%	1.40 [1.12 , 1.74]
Winhusen 2005	122	127	112	128	11.1%	1.10 [1.02 , 1.18]
Total (95% CI)		**2657**		**1557**	**100.0%**	**1.27 [1.19 , 1.37]**
Total events:	2094		998			

Heterogeneity: Tau² = 0.01; Chi² = 41.49, df = 13 (P < 0.0001); I² = 69%
Test for overall effect: Z = 6.64 (P < 0.00001)
Test for subgroup differences: Not applicable



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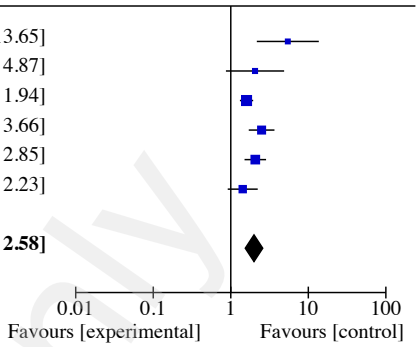
Analysis 2.10. Comparison 2: Extended-release methylphenidate versus placebo: harms (short term), Outcome 10: Psychiatric adverse events (proportion of participants)

Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Biederman 2003	26	109	5	114	6.4%	5.44 [2.17 , 13.65]
Casas 2008	23	181	6	97	7.1%	2.05 [0.87 , 4.87]
Compas 2007 CM	130	205	83	209	28.1%	1.60 [1.31 , 1.94]
Huss 2010	188	542	25	180	19.4%	2.50 [1.71 , 3.66]
Medori 2005	150	415	37	212	22.2%	2.07 [1.50 , 2.85]
Spencer 2003	71	165	16	53	16.8%	1.43 [0.91 , 2.23]
Total (95% CI)		**1617**		**865**	**100.0%**	**1.99 [1.54 , 2.58]**
Total events:	588		172			

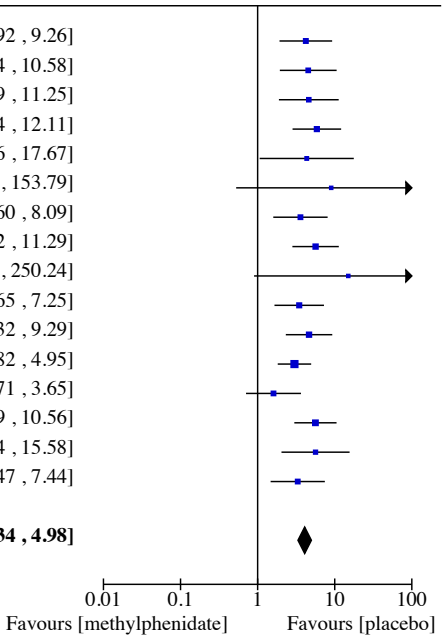
Heterogeneity: Tau² = 0.05; Chi² = 11.63, df = 5 (P = 0.04); I² = 57%
Test for overall effect: Z = 5.23 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.11. Comparison 2: Extended-release methylphenidate versus placebo: harms (short term), Outcome 11: Adverse event: Decreased appetite

Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Adler 2006	28	110	7	116	6.5%	4.22 [1.92 , 9.26]
Biederman 2003	26	109	6	114	5.6%	4.53 [1.94 , 10.58]
Casas 2008	43	181	5	97	5.0%	4.61 [1.89 , 11.25]
Compas 2007 CM	46	205	8	209	7.6%	5.86 [2.84 , 12.11]
Foquest 2014	33	297	2	78	2.0%	4.33 [1.06 , 17.67]
Ginsberg 2007	4	15	0	15	0.5%	9.00 [0.53 , 153.79]
Goodman 2009	25	174	7	175	6.1%	3.59 [1.60 , 8.09]
Huss 2010	136	542	8	180	8.4%	5.65 [2.82 , 11.29]
Konstenius 2007	7	27	0	27	0.5%	15.00 [0.90 , 250.24]
Medori 2005	77	305	7	96	7.3%	3.46 [1.65 , 7.25]
Retz 2008	40	84	8	78	8.3%	4.64 [2.32 , 9.29]
Rösler 2004	92	241	15	118	16.1%	3.00 [1.82 , 4.95]
Spencer 2003	30	165	6	53	6.0%	1.61 [0.71 , 3.65]
Takahashi 2011	57	143	10	141	10.1%	5.62 [2.99 , 10.56]
Weisler 2009	21	68	4	73	3.9%	5.64 [2.04 , 15.58]
Winhusen 2005	23	127	7	128	6.1%	3.31 [1.47 , 7.44]
Total (95% CI)		**2793**		**1698**	**100.0%**	**4.08 [3.34 , 4.98]**
Total events:	688		100			

Heterogeneity: Tau² = 0.00; Chi² = 11.53, df = 15 (P = 0.71); I² = 0%
Test for overall effect: Z = 13.75 (P < 0.00001)
Test for subgroup differences: Not applicable



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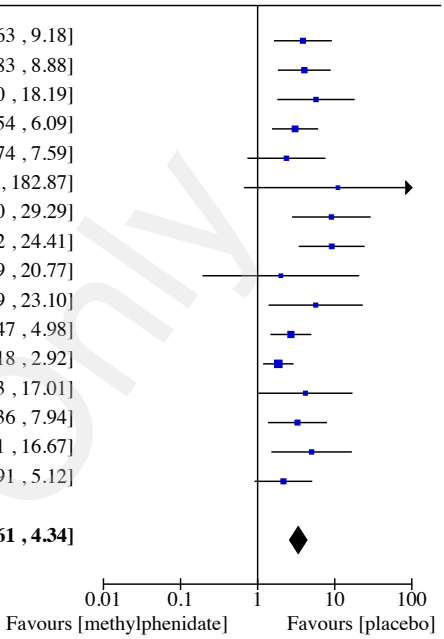
Analysis 2.12. Comparison 2: Extended-release methylphenidate versus placebo: harms (short term), Outcome 12: Adverse event: Dry mouth

Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Adler 2006	22	110	6	116	7.1%	3.87 [1.63 , 9.18]
Biederman 2003	27	109	7	114	8.3%	4.03 [1.83 , 8.88]
Casas 2008	32	181	3	97	4.3%	5.72 [1.80 , 18.19]
Compas 2007 CM	30	205	10	209	10.2%	3.06 [1.54 , 6.09]
Foquest 2014	27	297	3	78	4.3%	2.36 [0.74 , 7.59]
Ginsberg 2007	5	15	0	15	0.8%	11.00 [0.66 , 182.87]
Goodman 2009	27	174	3	175	4.2%	9.05 [2.80 , 29.29]
Huss 2010	110	542	4	180	5.8%	9.13 [3.42 , 24.41]
Konstenius 2007	2	27	1	27	1.2%	2.00 [0.19 , 20.77]
Medori 2005	36	305	2	96	3.0%	5.67 [1.39 , 23.10]
Retz 2008	32	84	11	78	12.1%	2.70 [1.47 , 4.98]
Rösler 2004	72	241	19	118	17.6%	1.86 [1.18 , 2.92]
Spencer 2003	26	165	2	53	3.0%	4.18 [1.03 , 17.01]
Takahashi 2011	20	143	6	141	6.9%	3.29 [1.36 , 7.94]
Weisler 2009	14	68	3	73	4.0%	5.01 [1.51 , 16.67]
Winhusen 2005	15	127	7	128	7.2%	2.16 [0.91 , 5.12]
Total (95% CI)		**2793**		**1698**	**100.0%**	**3.36 [2.61 , 4.34]**
Total events:	497		87			

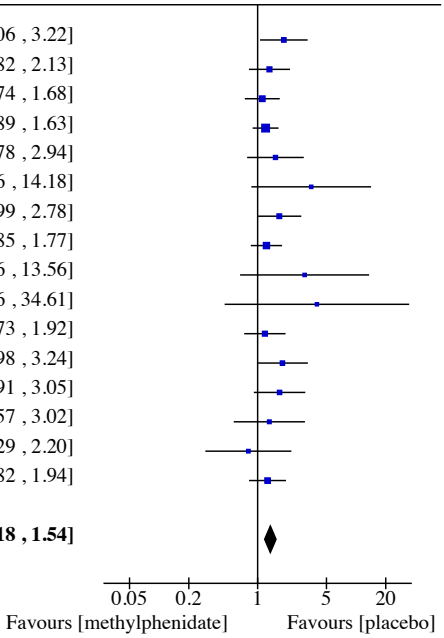
Heterogeneity: Tau² = 0.04; Chi² = 17.94, df = 15 (P = 0.27); I² = 16%
Test for overall effect: Z = 9.33 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.13. Comparison 2: Extended-release methylphenidate versus placebo: harms (short term), Outcome 13: Adverse event: Headache

Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Adler 2006	28	110	16	116	5.7%	1.85 [1.06 , 3.22]
Biederman 2003	29	109	23	114	7.6%	1.32 [0.82 , 2.13]
Casas 2008	52	181	25	97	10.6%	1.11 [0.74 , 1.68]
Compas 2007 CM	65	205	55	209	19.2%	1.20 [0.89 , 1.63]
Foquest 2014	52	297	9	78	4.0%	1.52 [0.78 , 2.94]
Ginsberg 2007	7	15	2	15	0.9%	3.50 [0.86 , 14.18]
Goodman 2009	33	174	20	175	6.7%	1.66 [0.99 , 2.78]
Huss 2010	111	542	30	180	13.1%	1.23 [0.85 , 1.77]
Konstenius 2007	6	27	2	27	0.8%	3.00 [0.66 , 13.56]
Levin 1998b	4	53	1	53	0.4%	4.00 [0.46 , 34.61]
Medori 2005	64	305	17	96	7.5%	1.18 [0.73 , 1.92]
Retz 2008	25	84	13	78	5.0%	1.79 [0.98 , 3.24]
Spencer 2003	52	165	10	53	4.9%	1.67 [0.91 , 3.05]
Takahashi 2011	12	143	9	141	2.5%	1.31 [0.57 , 3.02]
Weisler 2009	6	68	8	73	1.7%	0.81 [0.29 , 2.20]
Winhusen 2005	35	127	28	128	9.4%	1.26 [0.82 , 1.94]
Total (95% CI)		**2605**		**1633**	**100.0%**	**1.35 [1.18 , 1.54]**
Total events:	581		268			

Heterogeneity: Tau² = 0.00; Chi² = 10.16, df = 15 (P = 0.81); I² = 0%
Test for overall effect: Z = 4.39 (P < 0.0001)
Test for subgroup differences: Not applicable



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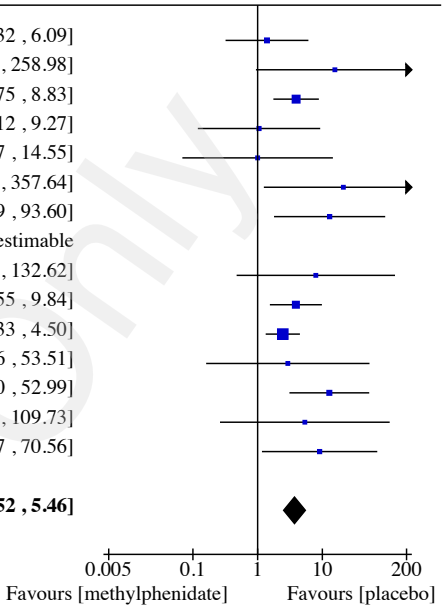
Analysis 2.15. Comparison 2: Extended-release methylphenidate versus placebo: harms (short term), Outcome 15: Adverse event: Palpitations

Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Biederman 2003	4	109	3	114	6.5%	1.39 [0.32 , 6.09]
Casas 2008	14	181	0	97	1.9%	15.62 [0.94 , 258.98]
Compas 2007 CM	27	205	7	209	19.4%	3.93 [1.75 , 8.83]
Foquest 2014	4	297	1	78	3.1%	1.05 [0.12 , 9.27]
Ginsberg 2007	1	15	1	15	2.0%	1.00 [0.07 , 14.55]
Goodman 2009	10	174	0	175	1.8%	21.12 [1.25 , 357.64]
Huss 2010	39	542	1	180	3.7%	12.95 [1.79 , 93.60]
Konstenius 2007	27	0	27	1		Not estimable
Medori 2005	12	305	0	96	1.8%	7.92 [0.47 , 132.62]
Retz 2008	21	84	5	78	15.3%	3.90 [1.55 , 9.84]
Rösler 2004	55	241	11	118	30.7%	2.45 [1.33 , 4.50]
Spencer 2003	4	165	0	53	1.7%	2.93 [0.16 , 53.51]
Takahashi 2011	26	143	2	141	7.0%	12.82 [3.10 , 52.99]
Weisler 2009	2	68	0	73	1.6%	5.36 [0.26 , 109.73]
Winhusen 2005	9	127	1	128	3.4%	9.07 [1.17 , 70.56]
Total (95% CI)		**2656**		**1556**	**100.0%**	**3.71 [2.52 , 5.46]**
Total events:	255		59			

Heterogeneity: Tau² = 0.03; Chi² = 13.72, df = 13 (P = 0.39); I² = 5%
Test for overall effect: Z = 6.66 (P < 0.00001)
Test for subgroup differences: Not applicable



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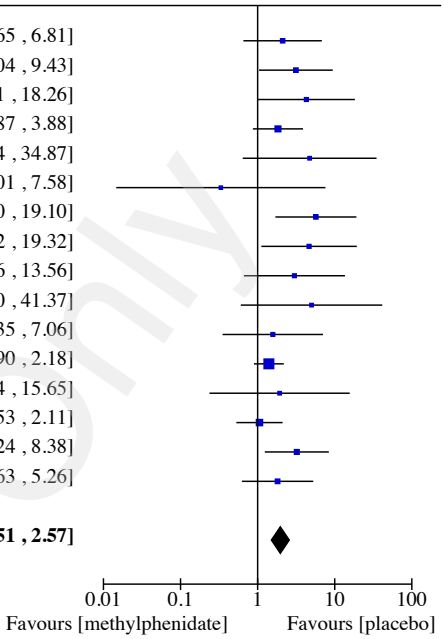
Analysis 2.16. Comparison 2: Extended-release methylphenidate versus placebo: harms (short term), Outcome 16: Adverse event: Insomnia

Study or Subgroup	Methylphenidate Events	Methylphenidate Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Adler 2006	8	110	4	116	5.0%	2.11 [0.65 , 6.81]
Biederman 2003	12	109	4	114	5.6%	3.14 [1.04 , 9.43]
Casas 2008	16	181	2	97	3.3%	4.29 [1.01 , 18.26]
Compas 2007 CM	18	205	10	209	11.5%	1.84 [0.87 , 3.88]
Foquest 2014	18	297	1	78	1.7%	4.73 [0.64 , 34.87]
Ginsberg 2007	0	15	1	15	0.7%	0.33 [0.01 , 7.58]
Goodman 2009	17	174	3	175	4.7%	5.70 [1.70 , 19.10]
Huss 2010	28	542	2	180	3.4%	4.65 [1.12 , 19.32]
Konstenius 2007	6	27	2	27	3.0%	3.00 [0.66 , 13.56]
Levin 1998b	5	53	1	53	1.6%	5.00 [0.60 , 41.37]
Medori 2005	10	305	2	96	3.1%	1.57 [0.35 , 7.06]
Rösler 2004	60	241	21	118	28.2%	1.40 [0.90 , 2.18]
Spencer 2003	6	165	1	53	1.6%	1.93 [0.24 , 15.65]
Takahashi 2011	15	143	14	141	13.4%	1.06 [0.53 , 2.11]
Weisler 2009	15	68	5	73	7.3%	3.22 [1.24 , 8.38]
Winhusen 2005	9	127	5	128	6.0%	1.81 [0.63 , 5.26]
Total (95% CI)		**2762**		**1673**	**100.0%**	**1.97 [1.51 , 2.57]**
Total events:	243		78			

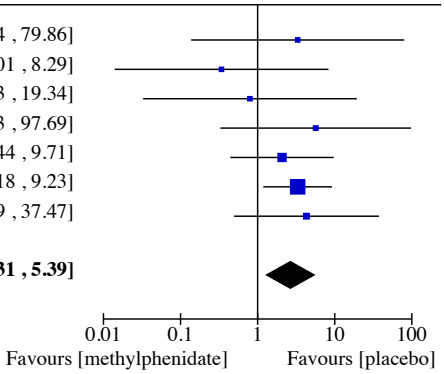
Heterogeneity: Tau² = 0.01; Chi² = 15.71, df = 15 (P = 0.40); I² = 4%
Test for overall effect: Z = 4.99 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.17. Comparison 2: Extended-release methylphenidate versus placebo: harms (short term), Outcome 17: Adverse event: Sexual dysfunction

Study or Subgroup	Methylphenidate Events	Methylphenidate Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Biederman 2003	1	67	0	74	4.9%	3.31 [0.14 , 79.86]
Compas 2007 CM	0	205	1	209	4.9%	0.34 [0.01 , 8.29]
Foquest 2014	1	297	0	78	4.9%	0.80 [0.03 , 19.34]
Huss 2010	8	542	0	180	6.2%	5.67 [0.33 , 97.69]
Medori 2005	8	596	2	309	21.0%	2.07 [0.44 , 9.71]
Rösler 2004	27	241	4	118	47.4%	3.30 [1.18 , 9.23]
Weisler 2009	4	68	1	73	10.7%	4.29 [0.49 , 37.47]
Total (95% CI)		**2016**		**1041**	**100.0%**	**2.66 [1.31 , 5.39]**
Total events:	49		8			

Heterogeneity: Tau² = 0.00; Chi² = 2.89, df = 6 (P = 0.82); I² = 0%
Test for overall effect: Z = 2.71 (P = 0.007)
Test for subgroup differences: Not applicable



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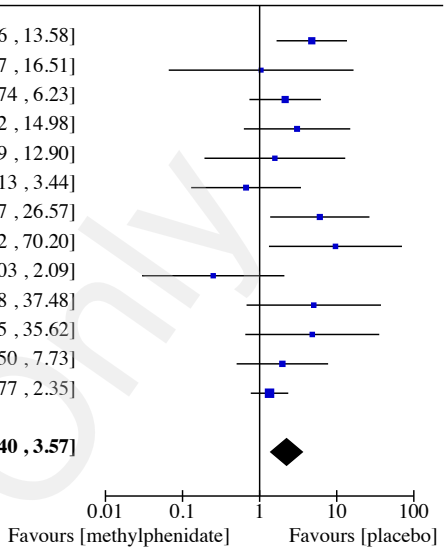
Analysis 2.18. Comparison 2: Extended-release methylphenidate versus placebo: harms (short term), Outcome 18: Adverse event: Anxiety

Study or Subgroup	Methylphenidate Events	Methylphenidate Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Adler 2006	18	110	4	116	12.1%	4.75 [1.66 , 13.58]
Biederman 2003	1	109	1	114	2.6%	1.05 [0.07 , 16.51]
Casas 2008	16	181	4	97	11.9%	2.14 [0.74 , 6.23]
Compas 2007 CM	6	205	2	209	6.8%	3.06 [0.62 , 14.98]
Foquest 2014	6	297	1	78	4.3%	1.58 [0.19 , 12.90]
Ginsberg 2007	2	15	3	15	6.5%	0.67 [0.13 , 3.44]
Goodman 2009	12	174	2	175	7.6%	6.03 [1.37 , 26.57]
Huss 2010	29	542	1	180	4.7%	9.63 [1.32 , 70.20]
Konstenius 2007	1	27	4	27	4.2%	0.25 [0.03 , 2.09]
Medori 2005	16	305	1	96	4.6%	5.04 [0.68 , 37.48]
Spencer 2003	15	165	1	53	4.7%	4.82 [0.65 , 35.62]
Takahashi 2011	6	143	3	141	8.5%	1.97 [0.50 , 7.73]
Winhusen 2005	24	127	18	128	21.5%	1.34 [0.77 , 2.35]
Total (95% CI)		**2400**		**1429**	**100.0%**	**2.23 [1.40 , 3.57]**
Total events:	152		45			

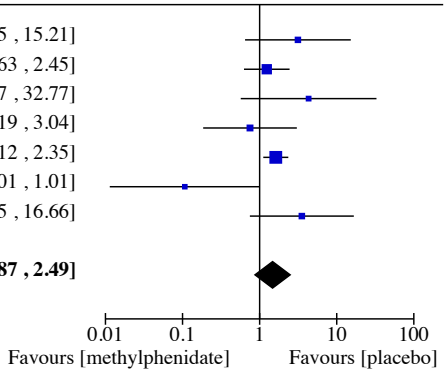
Heterogeneity: Tau² = 0.18; Chi² = 16.58, df = 12 (P = 0.17); I² = 28%
Test for overall effect: Z = 3.36 (P = 0.0008)
Test for subgroup differences: Not applicable



Analysis 2.19. Comparison 2: Extended-release methylphenidate versus placebo: harms (short term), Outcome 19: Adverse event: Depression

Study or Subgroup	Methylphenidate Events	Methylphenidate Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Biederman 2003	6	109	2	114	8.8%	3.14 [0.65 , 15.21]
Compas 2007 CM	17	205	14	209	25.1%	1.24 [0.63 , 2.45]
Huss 2010	13	542	1	180	5.8%	4.32 [0.57 , 32.77]
Konstenius 2007	3	27	4	27	10.6%	0.75 [0.19 , 3.04]
Medori 2005	100	596	32	309	35.7%	1.62 [1.12 , 2.35]
Spencer 2003	1	165	3	53	4.9%	0.11 [0.01 , 1.01]
Winhusen 2005	7	127	2	128	9.1%	3.53 [0.75 , 16.66]
Total (95% CI)		**1771**		**1020**	**100.0%**	**1.47 [0.87 , 2.49]**
Total events:	147		58			

Heterogeneity: Tau² = 0.16; Chi² = 9.78, df = 6 (P = 0.13); I² = 39%
Test for overall effect: Z = 1.44 (P = 0.15)
Test for subgroup differences: Not applicable



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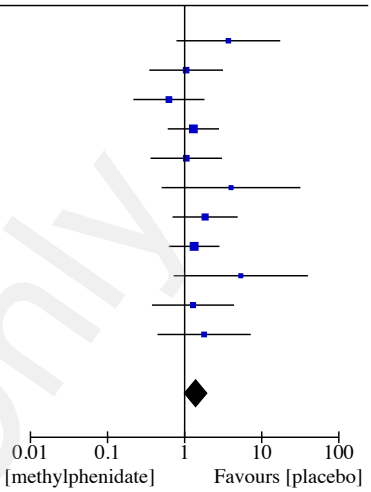
Analysis 2.20. Comparison 2: Extended-release methylphenidate versus placebo: harms (short term), Outcome 20: Adverse event: Irritability

Study or Subgroup	Methylphenidate Events	Methylphenidate Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Adler 2006	7	110	2	116	4.5%	3.69 [0.78 , 17.38]
Biederman 2003	6	109	6	114	9.0%	1.05 [0.35 , 3.14]
Casas 2008	7	181	6	97	9.7%	0.63 [0.22 , 1.81]
Compas 2007 CM	14	205	11	209	18.6%	1.30 [0.60 , 2.79]
Foquest 2014	16	297	4	78	9.6%	1.05 [0.36 , 3.05]
Ginsberg 2007	4	15	1	15	2.5%	4.00 [0.50 , 31.74]
Goodman 2009	11	174	6	175	11.5%	1.84 [0.70 , 4.88]
Huss 2010	32	542	8	180	19.0%	1.33 [0.62 , 2.83]
Medori 2005	17	305	1	96	2.7%	5.35 [0.72 , 39.68]
Spencer 2003	12	165	3	53	7.2%	1.28 [0.38 , 4.38]
Weisler 2009	5	68	3	73	5.6%	1.79 [0.44 , 7.20]
Total (95% CI)		**2171**		**1206**	**100.0%**	**1.39 [1.00 , 1.93]**
Total events:	131		51			

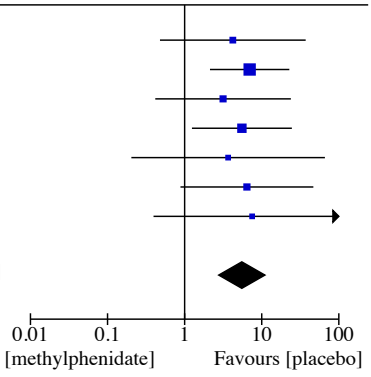
Heterogeneity: Tau² = 0.00; Chi² = 7.47, df = 10 (P = 0.68); I² = 0%
Test for overall effect: Z = 1.94 (P = 0.05)
Test for subgroup differences: Not applicable



Analysis 2.21. Comparison 2: Extended-release methylphenidate versus placebo: harms (short term), Outcome 21: Adverse event: Feeling jittery

Study or Subgroup	Methylphenidate Events	Methylphenidate Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Adler 2006	4	110	1	116	10.0%	4.22 [0.48 , 37.16]
Biederman 2003	20	109	3	114	33.8%	6.97 [2.13 , 22.80]
Foquest 2014	12	297	1	78	11.6%	3.15 [0.42 , 23.87]
Goodman 2009	11	174	2	175	21.3%	5.53 [1.24 , 24.59]
Huss 2010	5	542	0	180	5.7%	3.67 [0.20 , 65.99]
Spencer 2003	20	165	1	53	12.1%	6.42 [0.88 , 46.73]
Weisler 2009	3	68	0	73	5.5%	7.51 [0.39 , 142.71]
Total (95% CI)		**1465**		**789**	**100.0%**	**5.52 [2.77 , 10.99]**
Total events:	75		8			

Heterogeneity: Tau² = 0.00; Chi² = 0.64, df = 6 (P = 1.00); I² = 0%
Test for overall effect: Z = 4.86 (P < 0.00001)
Test for subgroup differences: Not applicable



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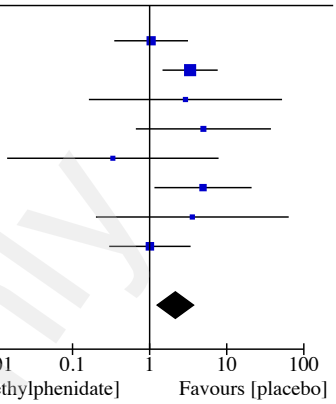
Analysis 2.22. Comparison 2: Extended-release methylphenidate versus placebo: harms (short term), Outcome 22: Adverse event: Agitation

Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Biederman 2003	6	109	6	114	20.6%	1.05 [0.35 , 3.14]
Compas 2007 CM	23	205	7	209	32.8%	3.35 [1.47 , 7.63]
Foquest 2014	5	297	0	78	3.4%	2.92 [0.16 , 52.18]
Huss 2010	15	542	1	180	6.8%	4.98 [0.66 , 37.45]
Konstenius 2007	0	27	1	27	2.9%	0.33 [0.01 , 7.84]
Medori 2005	19	596	2	309	12.6%	4.93 [1.15 , 21.01]
Spencer 2003	5	165	0	53	3.4%	3.58 [0.20 , 63.66]
Winhusen 2005	5	127	5	128	17.3%	1.01 [0.30 , 3.40]
Total (95% CI)		**2068**		**1098**	**100.0%**	**2.16 [1.25 , 3.71]**
Total events:	78		22			

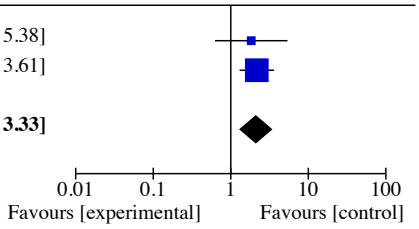
Heterogeneity: Tau² = 0.06; Chi² = 7.67, df = 7 (P = 0.36); I² = 9%
Test for overall effect: Z = 2.78 (P = 0.005)
Test for subgroup differences: Not applicable



Analysis 2.23. Comparison 2: Extended-release methylphenidate versus placebo: harms (short term), Outcome 23: Adverse event: aggression

Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Compas 2007 CM	9	205	5	209	18.4%	1.84 [0.63 , 5.38]
Medori 2005	71	596	17	309	81.6%	2.17 [1.30 , 3.61]
Total (95% CI)		**801**		**518**	**100.0%**	**2.10 [1.32 , 3.33]**
Total events:	80		22			

Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 3.15 (P = 0.002)
Test for subgroup differences: Not applicable



Comparison 3. Extended-release methylphenidate versus atomoxetine

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.1 Serious adverse events	1	142	Risk Ratio (IV, Random, 95% CI)	3.26 [0.14, 78.72]
3.2 Overall dropout	1	142	Risk Ratio (IV, Random, 95% CI)	0.71 [0.38, 1.31]
3.3 Adverse events: proportion experiencing any AE	1	142	Risk Ratio (IV, Random, 95% CI)	0.98 [0.85, 1.14]
3.4 Adverse events (leading to dropout)	1	142	Risk Ratio (IV, Random, 95% CI)	0.82 [0.30, 2.23]
3.5 ADHD symptoms (investigator rated)	1	141	Mean Difference (IV, Random, 95% CI)	-0.40 [-5.01, 4.21]

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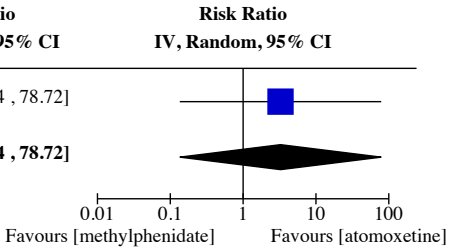
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.6 ADHD symptoms (self-rated)	1	142	Mean Difference (IV, Random, 95% CI)	-0.66 [-6.36, 5.04]
3.7 Adverse event: initial insomnia	1	142	Risk Ratio (IV, Random, 95% CI)	5.44 [1.65, 17.98]
3.8 Adverse event: headache	1	142	Risk Ratio (IV, Random, 95% CI)	0.47 [0.19, 1.14]
3.9 Adverse event: decreased appetite	1	142	Risk Ratio (IV, Random, 95% CI)	1.34 [0.78, 2.33]
3.10 Adverse event: irritability	1	142	Risk Ratio (IV, Random, 95% CI)	1.09 [0.33, 3.60]
3.11 Adverse event: dry mouth	1	142	Risk Ratio (IV, Random, 95% CI)	1.27 [0.63, 2.55]
3.12 Adverse event: decreased libido	1	142	Risk Ratio (IV, Random, 95% CI)	2.18 [0.41, 11.51]
3.13 Adverse event: feeling jittery	1	142	Risk Ratio (IV, Random, 95% CI)	0.82 [0.19, 3.52]
3.14 Adverse events: palpitations	1	142	Risk Ratio (IV, Random, 95% CI)	1.09 [0.16, 7.51]
3.15 Weight	1	142	Mean Difference (IV, Random, 95% CI)	-0.91 [-1.49, -0.33]

Analysis 3.1. Comparison 3: Extended-release methylphenidate versus atomoxetine, Outcome 1: Serious adverse events

Study or Subgroup	ER methylphenidate Events	ER methylphenidate Total	atomoxetine Events	atomoxetine Total	Weight	Risk Ratio IV, Random, 95% CI
Weisler 2009	1	68	0	74	100.0%	3.26 [0.14 , 78.72]
Total (95% CI)		**68**		**74**	**100.0%**	**3.26 [0.14 , 78.72]**
Total events:	1		0			

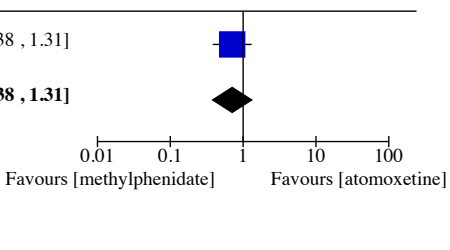
Heterogeneity: Not applicable
Test for overall effect: Z = 0.73 (P = 0.47)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Extended-release methylphenidate versus atomoxetine, Outcome 2: Overall dropout

Study or Subgroup	ER methylphenidate Events	ER methylphenidate Total	atomoxetine Events	atomoxetine Total	Weight	Risk Ratio IV, Random, 95% CI
Weisler 2009	13	68	20	74	100.0%	0.71 [0.38 , 1.31]
Total (95% CI)		**68**		**74**	**100.0%**	**0.71 [0.38 , 1.31]**
Total events:	13		20			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.10 (P = 0.27)
Test for subgroup differences: Not applicable



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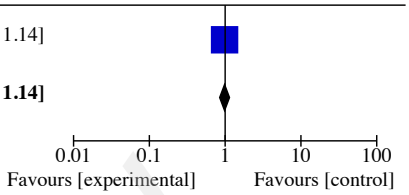
Analysis 3.3. Comparison 3: Extended-release methylphenidate versus atomoxetine, Outcome 3: Adverse events: proportion experiencing any AE

Study or Subgroup	ER methylphenidate Events	Total	atomoxetine Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Weisler 2009	56	68	62	74	100.0%	0.98 [0.85 , 1.14]
Total (95% CI)		**68**		**74**	**100.0%**	**0.98 [0.85 , 1.14]**
Total events:	56		62			

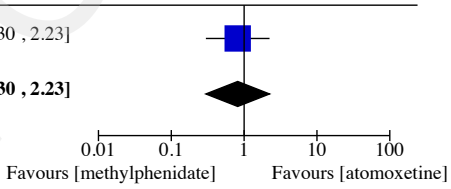
Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.82)
Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3: Extended-release methylphenidate versus atomoxetine, Outcome 4: Adverse events (leading to dropout)

Study or Subgroup	ER methylphenidate Events	Total	atomoxetine Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Weisler 2009	6	68	8	74	100.0%	0.82 [0.30 , 2.23]
Total (95% CI)		**68**		**74**	**100.0%**	**0.82 [0.30 , 2.23]**
Total events:	6		8			

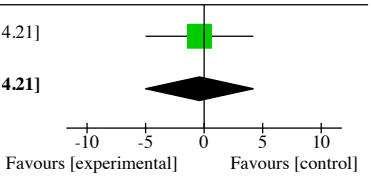
Heterogeneity: Not applicable
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3: Extended-release methylphenidate versus atomoxetine, Outcome 5: ADHD symptoms (investigator rated)

Study or Subgroup	ER methylphenidate Mean	SD	Total	atomoxetine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Weisler 2009	-15.7	13.39	68	-15.3	14.52	73	100.0%	-0.40 [-5.01 , 4.21]
Total (95% CI)			**68**			**73**	**100.0%**	**-0.40 [-5.01 , 4.21]**

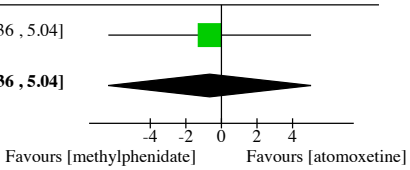
Heterogeneity: Not applicable
Test for overall effect: Z = 0.17 (P = 0.86)
Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3: Extended-release methylphenidate versus atomoxetine, Outcome 6: ADHD symptoms (self-rated)

Study or Subgroup	methylphenidate Mean	SD	Total	atomoxetine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Weisler 2009	-7.3	16.9385	68	-6.64	17.6967	74	100.0%	-0.66 [-6.36 , 5.04]
Total (95% CI)			**68**			**74**	**100.0%**	**-0.66 [-6.36 , 5.04]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.82)
Test for subgroup differences: Not applicable



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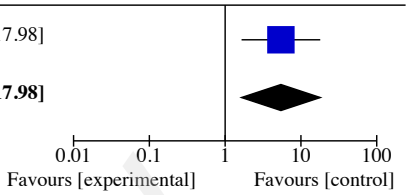
Analysis 3.7. Comparison 3: Extended-release methylphenidate versus atomoxetine, Outcome 7: Adverse event: initial insomnia

Study or Subgroup	ER methylphenidate Events	Total	atomoxetine Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Weisler 2009	15	68	3	74	100.0%	5.44 [1.65 , 17.98]
Total (95% CI)		**68**		**74**	**100.0%**	**5.44 [1.65 , 17.98]**
Total events:	15		3			

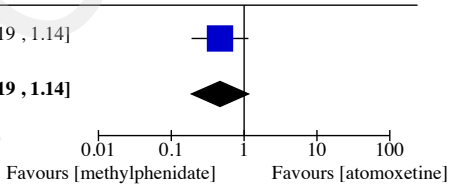
Heterogeneity: Not applicable
Test for overall effect: Z = 2.78 (P = 0.005)
Test for subgroup differences: Not applicable



Analysis 3.8. Comparison 3: Extended-release methylphenidate versus atomoxetine, Outcome 8: Adverse event: headache

Study or Subgroup	ER methylphenidate Events	Total	atomoxetine Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Weisler 2009	6	68	14	74	100.0%	0.47 [0.19 , 1.14]
Total (95% CI)		**68**		**74**	**100.0%**	**0.47 [0.19 , 1.14]**
Total events:	6		14			

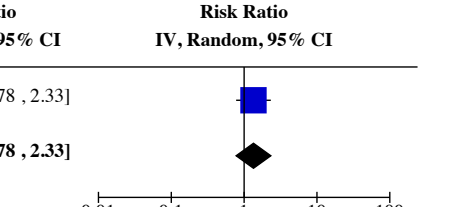
Heterogeneity: Not applicable
Test for overall effect: Z = 1.66 (P = 0.10)
Test for subgroup differences: Not applicable



Analysis 3.9. Comparison 3: Extended-release methylphenidate versus atomoxetine, Outcome 9: Adverse event: decreased appetite

Study or Subgroup	ER methylphenidate Events	Total	atomoxetine Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Weisler 2009	21	68	17	74	100.0%	1.34 [0.78 , 2.33]
Total (95% CI)		**68**		**74**	**100.0%**	**1.34 [0.78 , 2.33]**
Total events:	21		17			

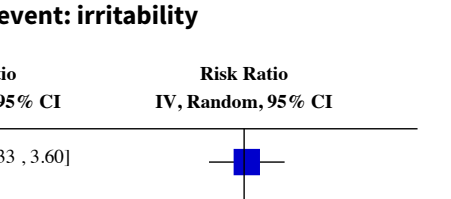
Heterogeneity: Not applicable
Test for overall effect: Z = 1.06 (P = 0.29)
Test for subgroup differences: Not applicable



Analysis 3.10. Comparison 3: Extended-release methylphenidate versus atomoxetine, Outcome 10: Adverse event: irritability

Study or Subgroup	ER methylphenidate Events	Total	atomoxetine Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Weisler 2009	5	68	5	74	100.0%	1.09 [0.33 , 3.60]
Total (95% CI)		**68**		**74**	**100.0%**	**1.09 [0.33 , 3.60]**
Total events:	5		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.14 (P = 0.89)
Test for subgroup differences: Not applicable



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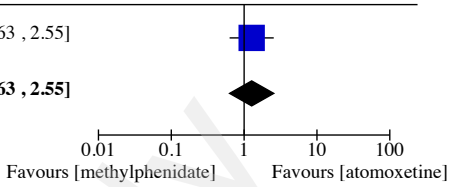
Analysis 3.11. Comparison 3: Extended-release methylphenidate versus atomoxetine, Outcome 11: Adverse event: dry mouth

Study or Subgroup	ER methylphenidate Events	Total	atomoxetine Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Weisler 2009	14	68	12	74	100.0%	1.27 [0.63 , 2.55]
Total (95% CI)		**68**		**74**	**100.0%**	**1.27 [0.63 , 2.55]**
Total events:	14		12			

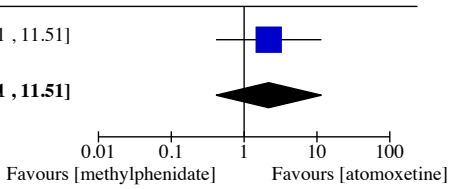
Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 3.12. Comparison 3: Extended-release methylphenidate versus atomoxetine, Outcome 12: Adverse event: decreased libido

Study or Subgroup	ER methylphenidate Events	Total	atomoxetine Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Weisler 2009	4	68	2	74	100.0%	2.18 [0.41 , 11.51]
Total (95% CI)		**68**		**74**	**100.0%**	**2.18 [0.41 , 11.51]**
Total events:	4		2			

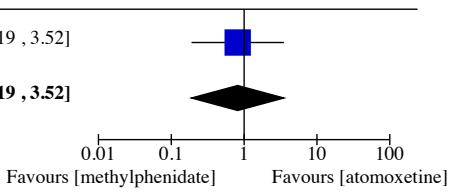
Heterogeneity: Not applicable
Test for overall effect: Z = 0.92 (P = 0.36)
Test for subgroup differences: Not applicable



Analysis 3.13. Comparison 3: Extended-release methylphenidate versus atomoxetine, Outcome 13: Adverse event: feeling jittery

Study or Subgroup	ER methylphenidate Events	Total	atomoxetine Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Weisler 2009	3	68	4	74	100.0%	0.82 [0.19 , 3.52]
Total (95% CI)		**68**		**74**	**100.0%**	**0.82 [0.19 , 3.52]**
Total events:	3		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.27 (P = 0.79)
Test for subgroup differences: Not applicable



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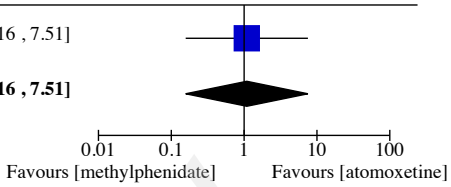
Analysis 3.14. Comparison 3: Extended-release methylphenidate versus atomoxetine, Outcome 14: Adverse events: palpitations

Study or Subgroup	ER methylphenidate Events	Total	atomoxetine Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Weisler 2009	2	68	2	74	100.0%	1.09 [0.16 , 7.51]
Total (95% CI)		**68**		**74**	**100.0%**	**1.09 [0.16 , 7.51]**
Total events:	2		2			

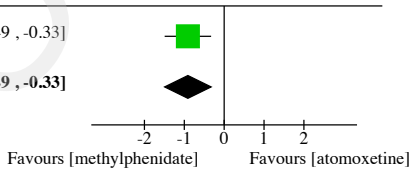
Heterogeneity: Not applicable
Test for overall effect: Z = 0.09 (P = 0.93)
Test for subgroup differences: Not applicable



Analysis 3.15. Comparison 3: Extended-release methylphenidate versus atomoxetine, Outcome 15: Weight

Study or Subgroup	ER methylphenidate Mean	SD	Total	atomoxetine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Weisler 2009	-1.47	1.934	68	-0.56	1.571	74	100.0%	-0.91 [-1.49 , -0.33]
Total (95% CI)			**68**			**74**	**100.0%**	**-0.91 [-1.49 , -0.33]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.06 (P = 0.002)
Test for subgroup differences: Not applicable



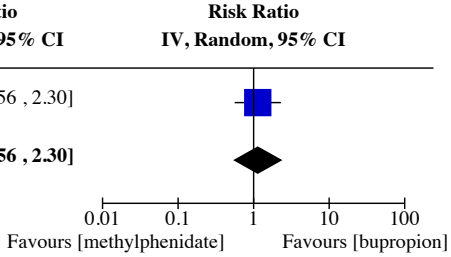
Comparison 4. Extended-release methylphenidate versus bupropion

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.1 Overall dropout	1	65	Risk Ratio (IV, Random, 95% CI)	1.13 [0.56, 2.30]
4.2 Dropouts due to adverse events	1	65	Risk Ratio (IV, Random, 95% CI)	3.09 [0.13, 73.19]
4.3 ADHD symptoms (self rated)	1	65	Mean Difference (IV, Random, 95% CI)	3.46 [-1.40, 8.32]

Analysis 4.1. Comparison 4: Extended-release methylphenidate versus bupropion, Outcome 1: Overall dropout

Study or Subgroup	methylphenidate Events	Total	bupropion Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Levin 1998a	11	32	10	33	100.0%	1.13 [0.56 , 2.30]
Total (95% CI)		**32**		**33**	**100.0%**	**1.13 [0.56 , 2.30]**
Total events:	11		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.73)
Test for subgroup differences: Not applicable



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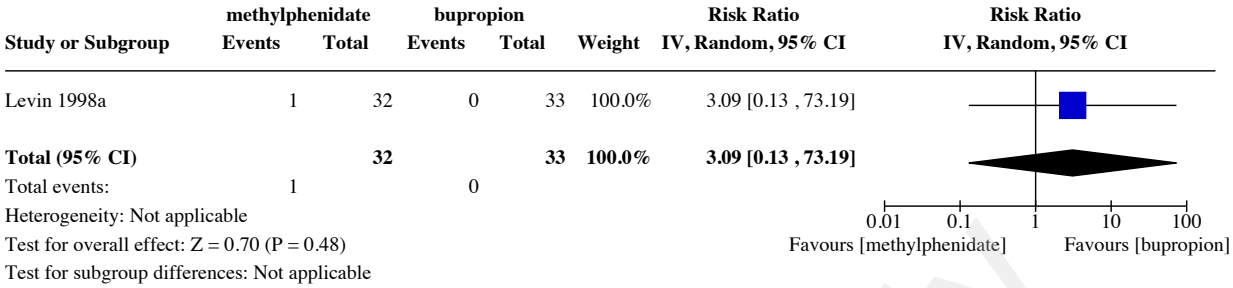
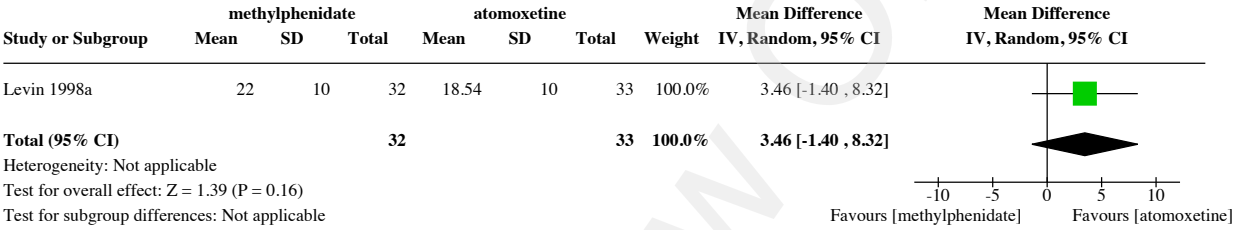
Analysis 4.2. Comparison 4: Extended-release methylphenidate versus bupropion, Outcome 2: Dropouts due to adverse events



Analysis 4.3. Comparison 4: Extended-release methylphenidate versus bupropion, Outcome 3: ADHD symptoms (self rated)



Comparison 5. Extended-release methylphenidate versus placebo (medium term)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Days missed at work/school/training (w13-26)	2	327	Mean Difference (IV, Random, 95% CI)	-0.42 [-2.48, 1.64]
5.2 Days missed at work/school/training (w26-52)	2	292	Mean Difference (IV, Random, 95% CI)	0.71 [-1.61, 3.03]
5.3 ADHD symptoms (self rated)	2	234	Mean Difference (IV, Random, 95% CI)	-1.59 [-4.26, 1.09]
5.4 ADHD symptoms (self rated) [LMCF data]	2	419	Mean Difference (IV, Random, 95% CI)	-2.23 [-3.50, -0.95]
5.5 ADHD symptoms (investigator rated)	2	243	Mean Difference (IV, Random, 95% CI)	-1.29 [-3.38, 0.80]
5.6 ADHD symptoms (investigator rated) [LMCF data]	2	419	Mean Difference (IV, Random, 95% CI)	-2.18 [-3.55, -0.80]
5.7 Quality of life (self rated)	2	419	Mean Difference (IV, Random, 95% CI)	-0.66 [-2.97, 1.64]

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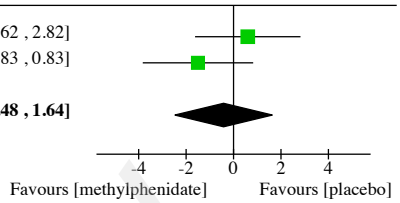
Analysis 5.1. Comparison 5: Extended-release methylphenidate versus placebo (medium term), Outcome 1: Days missed at work/school/training (w13-26)

Study or Subgroup	methylphenidate Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Compas 2007 CM	2.1	7.6	90	1.5	6.9	74	51.4%	0.60 [-1.62 , 2.82]
Compas 2007 GPT	1.3	4	88	2.8	9.6	75	48.6%	-1.50 [-3.83 , 0.83]
Total (95% CI)			**178**			**149**	**100.0%**	**-0.42 [-2.48 , 1.64]**

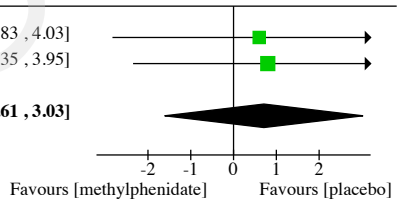
Heterogeneity: Tau² = 0.86; Chi² = 1.64, df = 1 (P = 0.20); I² = 39%
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable



Analysis 5.2. Comparison 5: Extended-release methylphenidate versus placebo (medium term), Outcome 2: Days missed at work/school/training (w26-52)

Study or Subgroup	methylphenidate Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Compas 2007 CM	4.3	11	81	3.7	9.7	60	45.7%	0.60 [-2.83 , 4.03]
Compas 2007 GPT	4	12.6	80	3.2	6.5	71	54.3%	0.80 [-2.35 , 3.95]
Total (95% CI)			**161**			**131**	**100.0%**	**0.71 [-1.61 , 3.03]**

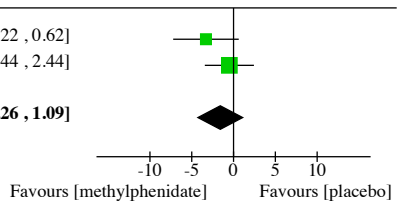
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)
Test for subgroup differences: Not applicable



Analysis 5.3. Comparison 5: Extended-release methylphenidate versus placebo (medium term), Outcome 3: ADHD symptoms (self rated)

Study or Subgroup	methylphenidate Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Compas 2007 CM	19.3	9.5	65	22.6	10.6	43	38.8%	-3.30 [-7.22 , 0.62]
Compas 2007 GPT	18.7	8.3	70	19.2	8.4	56	61.2%	-0.50 [-3.44 , 2.44]
Total (95% CI)			**135**			**99**	**100.0%**	**-1.59 [-4.26 , 1.09]**

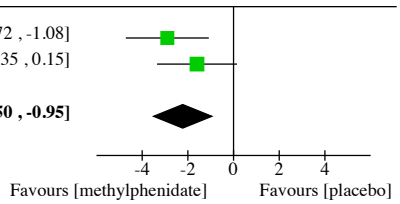
Heterogeneity: Tau² = 0.80; Chi² = 1.26, df = 1 (P = 0.26); I² = 20%
Test for overall effect: Z = 1.16 (P = 0.25)
Test for subgroup differences: Not applicable



Analysis 5.4. Comparison 5: Extended-release methylphenidate versus placebo (medium term), Outcome 4: ADHD symptoms (self rated) [LMCF data]

Study or Subgroup	methylphenidate Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Compas 2007 CM	15.1	6.7827	107	18	6.6517	103	48.1%	-2.90 [-4.72 , -1.08]
Compas 2007 GPT	15.3	6.14	103	16.9	6.7502	106	51.9%	-1.60 [-3.35 , 0.15]
Total (95% CI)			**210**			**209**	**100.0%**	**-2.23 [-3.50 , -0.95]**

Heterogeneity: Tau² = 0.02; Chi² = 1.02, df = 1 (P = 0.31); I² = 2%
Test for overall effect: Z = 3.43 (P = 0.0006)
Test for subgroup differences: Not applicable



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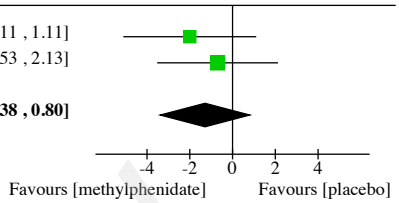
Analysis 5.5. Comparison 5: Extended-release methylphenidate versus placebo (medium term), Outcome 5: ADHD symptoms (investigator rated)

Study or Subgroup	methylphenidate Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Compas 2007 CM	19.2	8.6	70	21.2	8.1	45	45.2%	-2.00 [-5.11 , 1.11]
Compas 2007 GPT	18.2	7.8	69	18.9	8.4	59	54.8%	-0.70 [-3.53 , 2.13]
Total (95% CI)			**139**			**104**	**100.0%**	**-1.29 [-3.38 , 0.80]**

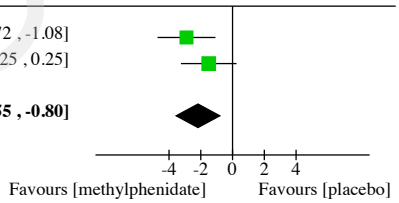
Heterogeneity: Tau² = 0.00; Chi² = 0.37, df = 1 (P = 0.54); I² = 0%
Test for overall effect: Z = 1.21 (P = 0.23)
Test for subgroup differences: Not applicable



Analysis 5.6. Comparison 5: Extended-release methylphenidate versus placebo (medium term), Outcome 6: ADHD symptoms (investigator rated) [LMCF data]

Study or Subgroup	methylphenidate Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Compas 2007 CM	14.6	6.2609	107	17.5	7.1633	103	48.2%	-2.90 [-4.72 , -1.08]
Compas 2007 GPT	14.9	6.6517	103	16.4	6.2309	106	51.8%	-1.50 [-3.25 , 0.25]
Total (95% CI)			**210**			**209**	**100.0%**	**-2.18 [-3.55 , -0.80]**

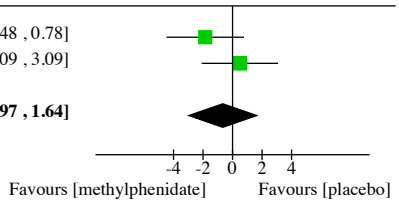
Heterogeneity: Tau² = 0.15; Chi² = 1.18, df = 1 (P = 0.28); I² = 15%
Test for overall effect: Z = 3.11 (P = 0.002)
Test for subgroup differences: Not applicable



Analysis 5.7. Comparison 5: Extended-release methylphenidate versus placebo (medium term), Outcome 7: Quality of life (self rated)

Study or Subgroup	methylphenidate Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Compas 2007 CM	-48.94	9.6523	107	-47.09	9.7728	103	49.5%	-1.85 [-4.48 , 0.78]
Compas 2007 GPT	-48.33	9.1588	103	-48.83	9.9175	106	50.5%	0.50 [-2.09 , 3.09]
Total (95% CI)			**210**			**209**	**100.0%**	**-0.66 [-2.97 , 1.64]**

Heterogeneity: Tau² = 0.99; Chi² = 1.56, df = 1 (P = 0.21); I² = 36%
Test for overall effect: Z = 0.56 (P = 0.57)
Test for subgroup differences: Not applicable



Comparison 6. Extended-release methylphenidate versus placebo: Subgroup and sensitivity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Overall dropout rate: Psychiatric co-morbidity (subgroup)	22		Risk Ratio (IV, Random, 95% CI)	Subtotals only
6.1.2 Low risk	1	54	Risk Ratio (IV, Random, 95% CI)	0.74 [0.53, 1.03]
6.1.3 Unclear risk	1	30	Risk Ratio (IV, Random, 95% CI)	Not estimable
6.1.4 High risk	20	4685	Risk Ratio (IV, Random, 95% CI)	1.04 [0.86, 1.25]

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Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6.2 Overall dropout rate: "Enriched de-sign" (subgroup)	22		Risk Ratio (IV, Random, 95% CI)	Subtotals only
6.2.2 Unclear risk	2	247	Risk Ratio (IV, Random, 95% CI)	1.02 [0.26, 3.98]
6.2.3 High risk	20	4522	Risk Ratio (IV, Random, 95% CI)	0.99 [0.83, 1.19]
6.3 Overall dropout rate: Withdrawl effects (subgroup)	22		Risk Ratio (IV, Random, 95% CI)	Subtotals only
6.3.1 Low risk	1	357	Risk Ratio (IV, Random, 95% CI)	0.91 [0.61, 1.34]
6.3.2 Unclear risk	5	822	Risk Ratio (IV, Random, 95% CI)	0.90 [0.62, 1.30]
6.3.3 High risk	16	3590	Risk Ratio (IV, Random, 95% CI)	1.07 [0.85, 1.34]
6.4 Overall dropout rate: Funding (sub-group)	22		Risk Ratio (IV, Random, 95% CI)	Subtotals only
6.4.1 Industry	13	3782	Risk Ratio (IV, Random, 95% CI)	1.14 [0.88, 1.47]
6.4.2 Public with industry-involvement	3	688	Risk Ratio (IV, Random, 95% CI)	0.73 [0.59, 0.91]
6.4.3 Public	5	279	Risk Ratio (IV, Random, 95% CI)	0.99 [0.70, 1.40]
6.4.4 Unclear funding	1	20	Risk Ratio (IV, Random, 95% CI)	0.33 [0.04, 2.69]
6.5 Proportion experiencing any adverse event: Psychiatric comorbidity (subgroup)	14		Risk Ratio (IV, Random, 95% CI)	Subtotals only
6.5.1 High	13	4184	Risk Ratio (IV, Random, 95% CI)	1.26 [1.18, 1.36]
6.5.2 Unclear	1	30	Risk Ratio (IV, Random, 95% CI)	2.40 [1.12, 5.13]
6.7 Proportion experiencing any adverse event: Withdrawal effects (subgroup)	14		Risk Ratio (IV, Random, 95% CI)	Subtotals only
6.7.1 High	11	3310	Risk Ratio (IV, Random, 95% CI)	1.28 [1.18, 1.38]
6.7.2 Unclear	2	555	Risk Ratio (IV, Random, 95% CI)	1.21 [0.95, 1.53]
6.7.3 Low	1	349	Risk Ratio (IV, Random, 95% CI)	1.46 [1.22, 1.74]
6.8 Proportion experiencing any adverse event: Funding (subgroup)	14		Risk Ratio (IV, Random, 95% CI)	Subtotals only
6.8.1 Industry	12	3545	Risk Ratio (IV, Random, 95% CI)	1.32 [1.23, 1.41]
6.8.2 Public with industry-involvement	2	669	Risk Ratio (IV, Random, 95% CI)	1.09 [1.05, 1.14]
6.9 Proportion experiencing any adverse event: Dropout rates (sensitivity)	14		Risk Ratio (IV, Random, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6.9.1 High	10	3363	Risk Ratio (IV, Random, 95% CI)	1.21 [1.14, 1.29]
6.9.2 Unclear	1	375	Risk Ratio (IV, Random, 95% CI)	1.46 [1.12, 1.89]
6.9.3 Low	3	476	Risk Ratio (IV, Random, 95% CI)	1.56 [1.35, 1.81]

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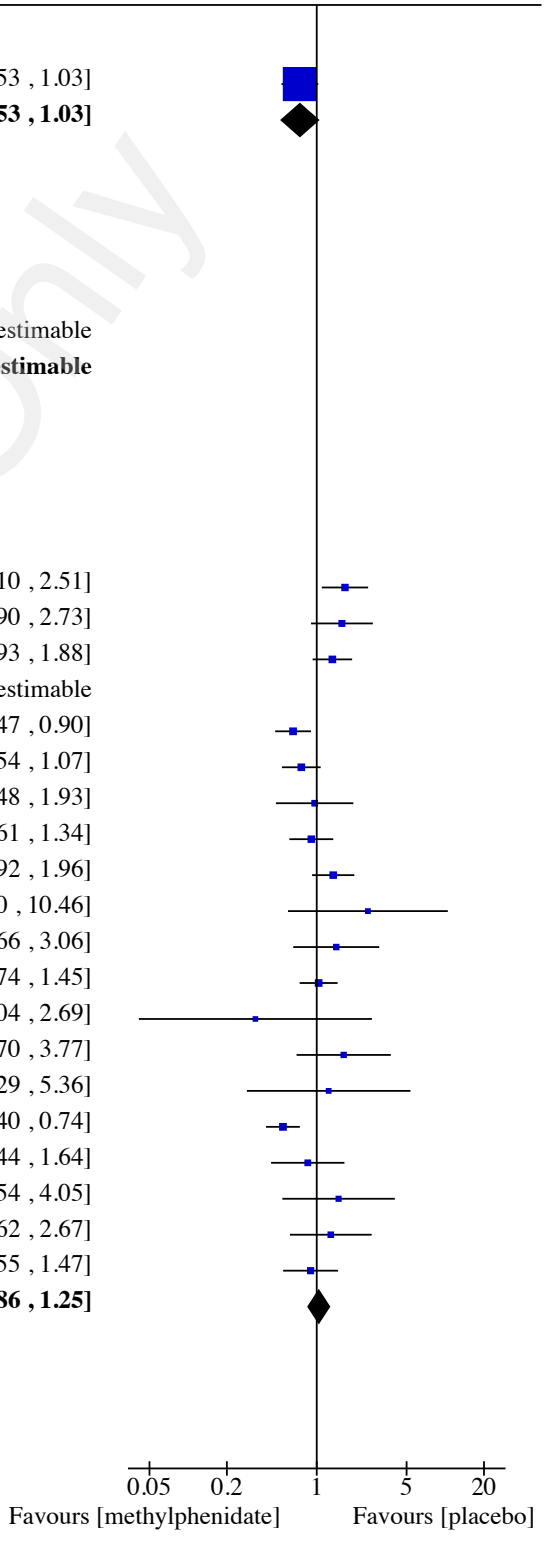
Analysis 6.1. Comparison 6: Extended-release methylphenidate versus placebo: Subgroup and sensitivity, Outcome 1: Overall dropout rate: Psychiatric comorbidity (subgroup)

Study or Subgroup	methylphenidate Events	Total	placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
6.1.2 Low risk						
Konstenius 2007	17	27	23	27	100.0%	0.74 [0.53 , 1.03]
Subtotal (95% CI)		**27**		**27**	**100.0%**	**0.74 [0.53 , 1.03]**
Total events:	17		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.80 (P = 0.07)						
6.1.3 Unclear risk						
Ginsberg 2007	0	15	0	15		Not estimable
Subtotal (95% CI)		**15**		**15**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
6.1.4 High risk						
Adler 2006	42	113	26	116	7.0%	1.66 [1.10 , 2.51]
Biederman 2003	26	112	17	115	5.5%	1.57 [0.90 , 2.73]
Casas 2008	72	182	29	97	7.7%	1.32 [0.93 , 1.88]
Chronis-Tuscano 2004	0	9	0	11		Not estimable
Compas 2007 CM	37	110	55	107	8.1%	0.65 [0.47 , 0.90]
Compas 2007 GPT	35	107	47	109	7.8%	0.76 [0.54 , 1.07]
Foquest 2014	33	297	9	78	4.4%	0.96 [0.48 , 1.93]
Goodman 2009	37	178	41	179	7.3%	0.91 [0.61 , 1.34]
Huss 2010	113	544	28	181	7.4%	1.34 [0.92 , 1.96]
Konstenius 2006	5	12	2	12	1.5%	2.50 [0.60 , 10.46]
Levin 1998a	11	32	8	33	3.8%	1.42 [0.66 , 3.06]
Levin 1998b	30	53	29	53	7.9%	1.03 [0.74 , 1.45]
Levin 2001	1	10	3	10	0.8%	0.33 [0.04 , 2.69]
Medori 2005	31	306	6	96	3.4%	1.62 [0.70 , 3.77]
Retz 2008	4	84	3	78	1.4%	1.24 [0.29 , 5.36]
Rösler 2004	58	241	52	118	8.3%	0.55 [0.40 , 0.74]
Spencer 2003	27	168	10	53	4.6%	0.85 [0.44 , 1.64]
Takahashi 2011	9	143	6	141	2.6%	1.48 [0.54 , 4.05]
Weisler 2009	13	68	11	74	4.1%	1.29 [0.62 , 2.67]
Winhusen 2005	24	127	27	128	6.2%	0.90 [0.55 , 1.47]
Subtotal (95% CI)		**2896**		**1789**	**100.0%**	**1.04 [0.86 , 1.25]**
Total events:	608		409			
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 43.57$, df = 18 (P = 0.0007); $I^2 = 59\%$						
Test for overall effect: Z = 0.38 (P = 0.71)						
Test for subgroup differences: $Chi^2 = 3.06$, df = 1 (P = 0.08), $I^2 = 67.3\%$						



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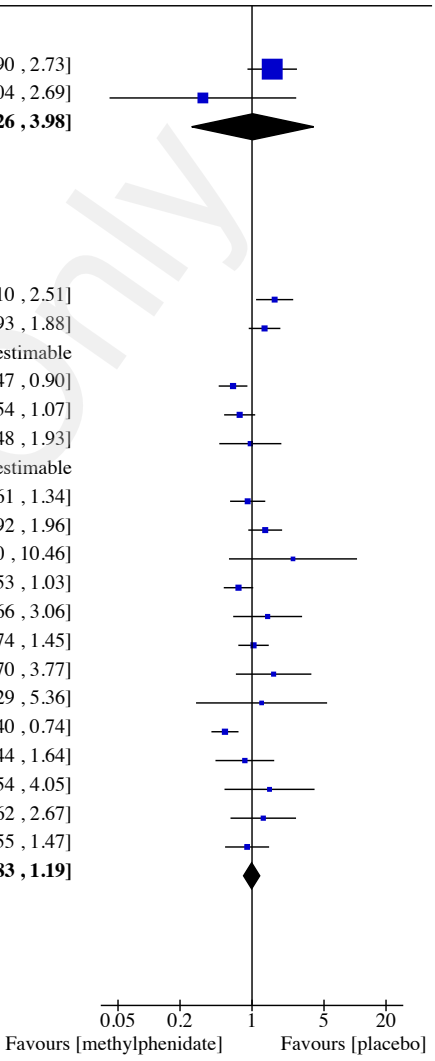
Analysis 6.2. Comparison 6: Extended-release methylphenidate versus placebo: Subgroup and sensitivity, Outcome 2: Overall dropout rate: "Enriched design" (subgroup)

Study or Subgroup	methylphenidate Events	Total	placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
6.2.2 Unclear risk						
Biederman 2003	26	112	17	115	71.9%	1.57 [0.90 , 2.73]
Levin 2001	1	10	3	10	28.1%	0.33 [0.04 , 2.69]
Subtotal (95% CI)		**122**		**125**	**100.0%**	**1.02 [0.26 , 3.98]**
Total events:	27		20			
Heterogeneity: Tau² = 0.59; Chi² = 1.98, df = 1 (P = 0.16); I² = 50%						
Test for overall effect: Z = 0.02 (P = 0.98)						
6.2.3 High risk						
Adler 2006	42	113	26	116	6.9%	1.66 [1.10 , 2.51]
Casas 2008	72	182	29	97	7.7%	1.32 [0.93 , 1.88]
Chronis-Tuscano 2004	0	9	0	11		Not estimable
Compas 2007 CM	37	110	55	107	8.1%	0.65 [0.47 , 0.90]
Compas 2007 GPT	35	107	47	109	7.8%	0.76 [0.54 , 1.07]
Foquest 2014	33	297	9	78	4.2%	0.96 [0.48 , 1.93]
Ginsberg 2007	0	15	0	15		Not estimable
Goodman 2009	37	178	41	179	7.2%	0.91 [0.61 , 1.34]
Huss 2010	113	544	28	181	7.4%	1.34 [0.92 , 1.96]
Konstenius 2006	5	12	2	12	1.4%	2.50 [0.60 , 10.46]
Konstenius 2007	17	27	23	27	8.0%	0.74 [0.53 , 1.03]
Levin 1998a	11	32	8	33	3.7%	1.42 [0.66 , 3.06]
Levin 1998b	30	53	29	53	7.9%	1.03 [0.74 , 1.45]
Medori 2005	31	306	6	96	3.2%	1.62 [0.70 , 3.77]
Retz 2008	4	84	3	78	1.3%	1.24 [0.29 , 5.36]
Rösler 2004	58	241	52	118	8.4%	0.55 [0.40 , 0.74]
Spencer 2003	27	168	10	53	4.5%	0.85 [0.44 , 1.64]
Takahashi 2011	9	143	6	141	2.5%	1.48 [0.54 , 4.05]
Weisler 2009	13	68	11	74	3.9%	1.29 [0.62 , 2.67]
Winhusen 2005	24	127	27	128	6.0%	0.90 [0.55 , 1.47]
Subtotal (95% CI)		**2816**		**1706**	**100.0%**	**0.99 [0.83 , 1.19]**
Total events:	598		412			
Heterogeneity: Tau² = 0.08; Chi² = 41.45, df = 17 (P = 0.0008); I² = 59%						
Test for overall effect: Z = 0.09 (P = 0.93)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² = 0%						



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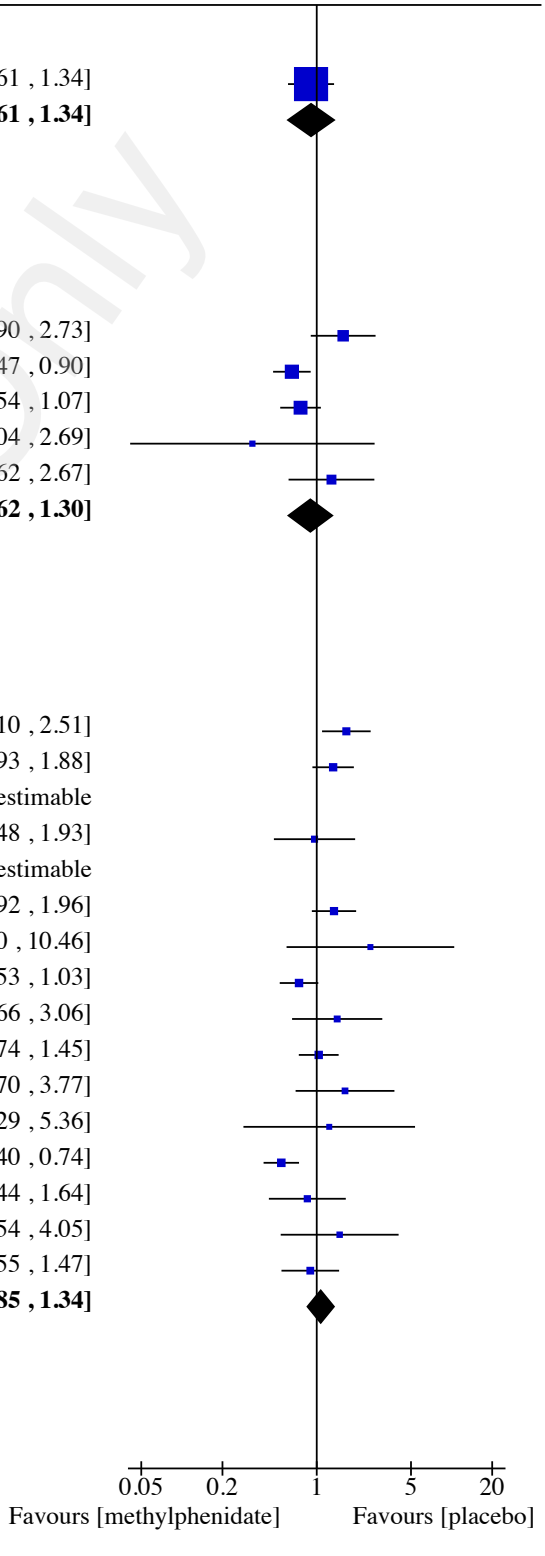
Analysis 6.3. Comparison 6: Extended-release methylphenidate versus placebo: Subgroup and sensitivity, Outcome 3: Overall dropout rate: Withdrawl effects (subgroup)

Study or Subgroup	methylphenidate Events	Total	placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
6.3.1 Low risk						
Goodman 2009	37	178	41	179	100.0%	0.91 [0.61 , 1.34]
Subtotal (95% CI)		**178**		**179**	**100.0%**	**0.91 [0.61 , 1.34]**
Total events:	37		41			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (P = 0.63)						
6.3.2 Unclear risk						
Biederman 2003	26	112	17	115	21.2%	1.57 [0.90 , 2.73]
Compas 2007 CM	37	110	55	107	30.6%	0.65 [0.47 , 0.90]
Compas 2007 GPT	35	107	47	109	29.5%	0.76 [0.54 , 1.07]
Levin 2001	1	10	3	10	3.0%	0.33 [0.04 , 2.69]
Weisler 2009	13	68	11	74	15.7%	1.29 [0.62 , 2.67]
Subtotal (95% CI)		**407**		**415**	**100.0%**	**0.90 [0.62 , 1.30]**
Total events:	112		133			
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 9.56$, df = 4 (P = 0.05); $I^2 = 58\%$						
Test for overall effect: Z = 0.57 (P = 0.57)						
6.3.3 High risk						
Adler 2006	42	113	26	116	9.4%	1.66 [1.10 , 2.51]
Casas 2008	72	182	29	97	10.3%	1.32 [0.93 , 1.88]
Chronis-Tuscano 2004	0	9	0	11		Not estimable
Foquest 2014	33	297	9	78	6.0%	0.96 [0.48 , 1.93]
Ginsberg 2007	0	15	0	15		Not estimable
Huss 2010	113	544	28	181	9.9%	1.34 [0.92 , 1.96]
Konstenius 2006	5	12	2	12	2.1%	2.50 [0.60 , 10.46]
Konstenius 2007	17	27	23	27	10.6%	0.74 [0.53 , 1.03]
Levin 1998a	11	32	8	33	5.3%	1.42 [0.66 , 3.06]
Levin 1998b	30	53	29	53	10.5%	1.03 [0.74 , 1.45]
Medori 2005	31	306	6	96	4.7%	1.62 [0.70 , 3.77]
Retz 2008	4	84	3	78	2.0%	1.24 [0.29 , 5.36]
Rösler 2004	58	241	52	118	11.0%	0.55 [0.40 , 0.74]
Spencer 2003	27	168	10	53	6.3%	0.85 [0.44 , 1.64]
Takahashi 2011	9	143	6	141	3.7%	1.48 [0.54 , 4.05]
Winhusen 2005	24	127	27	128	8.3%	0.90 [0.55 , 1.47]
Subtotal (95% CI)		**2353**		**1237**	**100.0%**	**1.07 [0.85 , 1.34]**
Total events:	476		258			
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 33.77$, df = 13 (P = 0.001); $I^2 = 62\%$						
Test for overall effect: Z = 0.59 (P = 0.56)						
Test for subgroup differences: $Chi^2 = 0.91$, df = 2 (P = 0.64), $I^2 = 0\%$						



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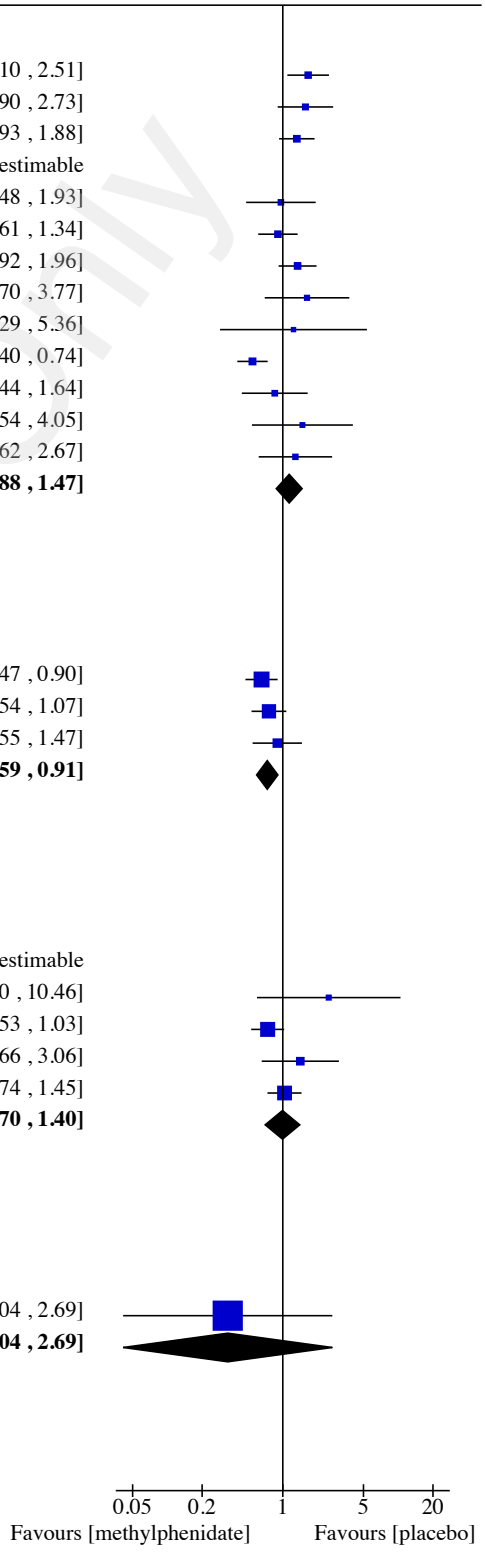
Analysis 6.4. Comparison 6: Extended-release methylphenidate versus placebo: Subgroup and sensitivity, Outcome 4: Overall dropout rate: Funding (subgroup)

Study or Subgroup	methylphenidate Events	Total	placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
6.4.1 Industry						
Adler 2006	42	113	26	116	10.7%	1.66 [1.10 , 2.51]
Biederman 2003	26	112	17	115	8.8%	1.57 [0.90 , 2.73]
Casas 2008	72	182	29	97	11.6%	1.32 [0.93 , 1.88]
Chronis-Tuscano 2004	0	9	0	11		Not estimable
Foquest 2014	33	297	9	78	7.1%	0.96 [0.48 , 1.93]
Goodman 2009	37	178	41	179	11.0%	0.91 [0.61 , 1.34]
Huss 2010	113	544	28	181	11.2%	1.34 [0.92 , 1.96]
Medori 2005	31	306	6	96	5.7%	1.62 [0.70 , 3.77]
Retz 2008	4	84	3	78	2.6%	1.24 [0.29 , 5.36]
Rösler 2004	58	241	52	118	12.3%	0.55 [0.40 , 0.74]
Spencer 2003	27	168	10	53	7.6%	0.85 [0.44 , 1.64]
Takahashi 2011	9	143	6	141	4.5%	1.48 [0.54 , 4.05]
Weisler 2009	13	68	11	74	6.7%	1.29 [0.62 , 2.67]
Subtotal (95% CI)		**2445**		**1337**	**100.0%**	**1.14 [0.88 , 1.47]**
Total events:	465		238			
Heterogeneity: Tau² = 0.12; Chi² = 30.66, df = 11 (P = 0.001); I² = 64%						
Test for overall effect: Z = 0.97 (P = 0.33)						
6.4.2 Public with industry-involvement						
Compas 2007 CM	37	110	55	107	43.9%	0.65 [0.47 , 0.90]
Compas 2007 GPT	35	107	47	109	37.5%	0.76 [0.54 , 1.07]
Winhusen 2005	24	127	27	128	18.6%	0.90 [0.55 , 1.47]
Subtotal (95% CI)		**344**		**344**	**100.0%**	**0.73 [0.59 , 0.91]**
Total events:	96		129			
Heterogeneity: Tau² = 0.00; Chi² = 1.16, df = 2 (P = 0.56); I² = 0%						
Test for overall effect: Z = 2.86 (P = 0.004)						
6.4.3 Public						
Ginsberg 2007	0	15	0	15		Not estimable
Konstenius 2006	5	12	2	12	5.3%	2.50 [0.60 , 10.46]
Konstenius 2007	17	27	23	27	40.2%	0.74 [0.53 , 1.03]
Levin 1998a	11	32	8	33	15.2%	1.42 [0.66 , 3.06]
Levin 1998b	30	53	29	53	39.3%	1.03 [0.74 , 1.45]
Subtotal (95% CI)		**139**		**140**	**100.0%**	**0.99 [0.70 , 1.40]**
Total events:	63		62			
Heterogeneity: Tau² = 0.05; Chi² = 5.23, df = 3 (P = 0.16); I² = 43%						
Test for overall effect: Z = 0.04 (P = 0.97)						
6.4.4 Unclear funding						
Levin 2001	1	10	3	10	100.0%	0.33 [0.04 , 2.69]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**0.33 [0.04 , 2.69]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.03 (P = 0.30)						
Test for subgroup differences: Chi² = 7.88, df = 3 (P = 0.05), I² = 61.9%						



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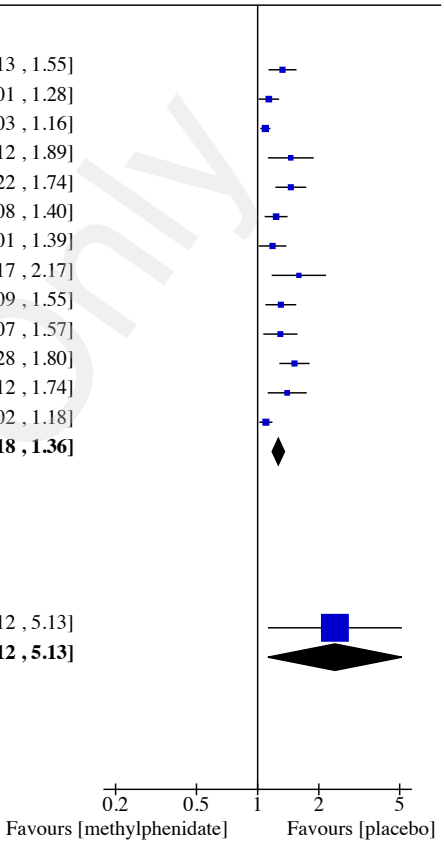
Analysis 6.5. Comparison 6: Extended-release methylphenidate versus placebo: Subgroup and sensitivity, Outcome 5: Proportion experiencing any adverse event: Psychiatric comorbidity (subgroup)

Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
6.5.1 High						
Adler 2006	93	110	74	116	7.8%	1.33 [1.13 , 1.55]
Casas 2008	161	181	76	97	9.6%	1.14 [1.01 , 1.28]
Compas 2007 CM	197	205	184	209	12.1%	1.09 [1.03 , 1.16]
Foquest 2014	194	297	35	78	4.6%	1.46 [1.12 , 1.89]
Goodman 2009	126	174	87	175	7.2%	1.46 [1.22 , 1.74]
Huss 2010	401	542	108	180	9.0%	1.23 [1.08 , 1.40]
Medori 2005	237	305	63	96	7.9%	1.18 [1.01 , 1.39]
Retz 2008	55	84	32	78	3.7%	1.60 [1.17 , 2.17]
Rösler 2004	178	241	67	118	7.2%	1.30 [1.09 , 1.55]
Spencer 2003	145	165	36	53	6.5%	1.29 [1.07 , 1.57]
Takahashi 2011	117	143	76	141	7.3%	1.52 [1.28 , 1.80]
Weisler 2009	56	68	43	73	5.7%	1.40 [1.12 , 1.74]
Winhusen 2005	122	127	112	128	11.4%	1.10 [1.02 , 1.18]
Subtotal (95% CI)		**2642**		**1542**	**100.0%**	**1.26 [1.18 , 1.36]**
Total events:	2082		993			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 38.12$, df = 12 (P = 0.0001); $I^2 = 69\%$						
Test for overall effect: Z = 6.61 (P < 0.00001)						
6.5.2 Unclear						
Ginsberg 2007	12	15	5	15	100.0%	2.40 [1.12 , 5.13]
Subtotal (95% CI)		**15**		**15**	**100.0%**	**2.40 [1.12 , 5.13]**
Total events:	12		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.26 (P = 0.02)						
Test for subgroup differences: $Chi^2 = 2.72$, df = 1 (P = 0.10), $I^2 = 63.2\%$						



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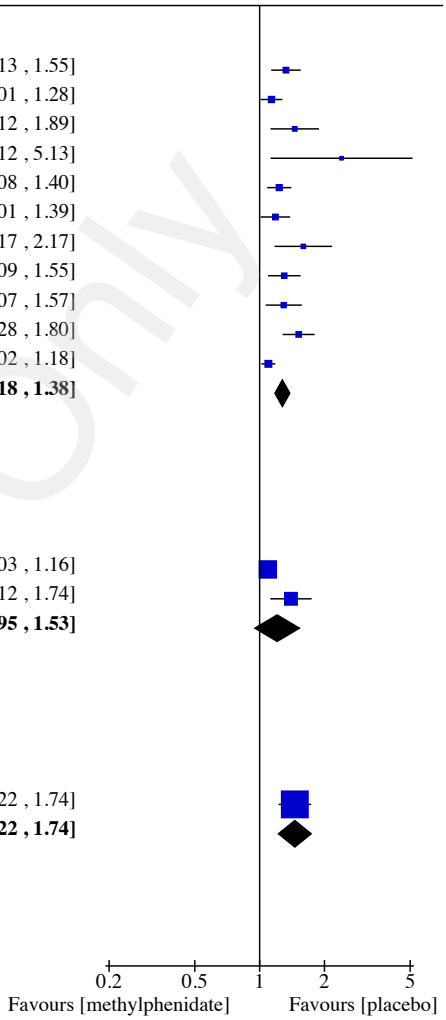
Analysis 6.7. Comparison 6: Extended-release methylphenidate versus placebo: Subgroup and sensitivity, Outcome 7: Proportion experiencing any adverse event: Withdrawal effects (subgroup)

Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
6.7.1 High						
Adler 2006	93	110	74	116	10.3%	1.33 [1.13 , 1.55]
Casas 2008	161	181	76	97	12.7%	1.14 [1.01 , 1.28]
Foquest 2014	194	297	35	78	6.1%	1.46 [1.12 , 1.89]
Ginsberg 2007	12	15	5	15	1.0%	2.40 [1.12 , 5.13]
Huss 2010	401	542	108	180	11.9%	1.23 [1.08 , 1.40]
Medori 2005	237	305	63	96	10.4%	1.18 [1.01 , 1.39]
Retz 2008	55	84	32	78	4.8%	1.60 [1.17 , 2.17]
Rösler 2004	178	241	67	118	9.5%	1.30 [1.09 , 1.55]
Spencer 2003	145	165	36	53	8.6%	1.29 [1.07 , 1.57]
Takahashi 2011	117	143	76	141	9.6%	1.52 [1.28 , 1.80]
Winhusen 2005	122	127	112	128	15.1%	1.10 [1.02 , 1.18]
Subtotal (95% CI)		**2210**		**1100**	**100.0%**	**1.28 [1.18 , 1.38]**
Total events:	1715		684			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 25.19$, df = 10 (P = 0.005); $I^2 = 60\%$						
Test for overall effect: Z = 6.01 (P < 0.00001)						
6.7.2 Unclear						
Compas 2007 CM	197	205	184	209	59.7%	1.09 [1.03 , 1.16]
Weisler 2009	56	68	43	73	40.3%	1.40 [1.12 , 1.74]
Subtotal (95% CI)		**273**		**282**	**100.0%**	**1.21 [0.95 , 1.53]**
Total events:	253		227			
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 4.52$, df = 1 (P = 0.03); $I^2 = 78\%$						
Test for overall effect: Z = 1.54 (P = 0.12)						
6.7.3 Low						
Goodman 2009	126	174	87	175	100.0%	1.46 [1.22 , 1.74]
Subtotal (95% CI)		**174**		**175**	**100.0%**	**1.46 [1.22 , 1.74]**
Total events:	126		87			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.21 (P < 0.0001)						
Test for subgroup differences: $Chi^2 = 2.22$, df = 2 (P = 0.33), $I^2 = 10.0\%$						



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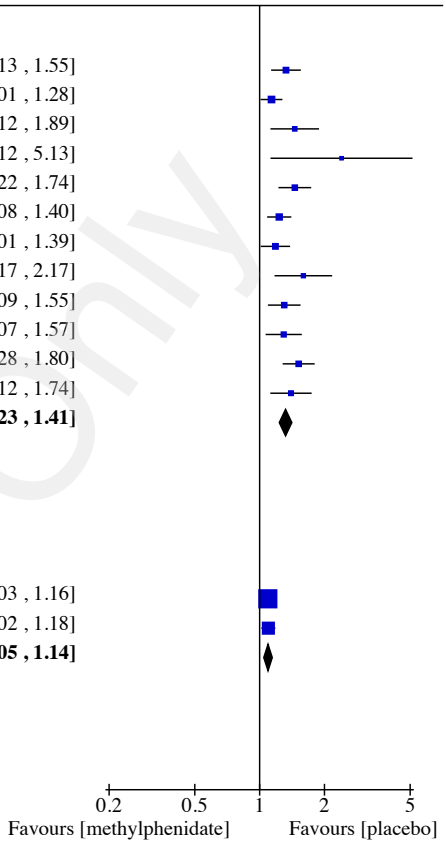
Analysis 6.8. Comparison 6: Extended-release methylphenidate versus placebo: Subgroup and sensitivity, Outcome 8: Proportion experiencing any adverse event: Funding (subgroup)

Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
6.8.1 Industry						
Adler 2006	93	110	74	116	10.3%	1.33 [1.13 , 1.55]
Casas 2008	161	181	76	97	14.0%	1.14 [1.01 , 1.28]
Foquest 2014	194	297	35	78	5.2%	1.46 [1.12 , 1.89]
Ginsberg 2007	12	15	5	15	0.8%	2.40 [1.12 , 5.13]
Goodman 2009	126	174	87	175	9.2%	1.46 [1.22 , 1.74]
Huss 2010	401	542	108	180	12.8%	1.23 [1.08 , 1.40]
Medori 2005	237	305	63	96	10.4%	1.18 [1.01 , 1.39]
Retz 2008	55	84	32	78	4.0%	1.60 [1.17 , 2.17]
Rösler 2004	178	241	67	118	9.2%	1.30 [1.09 , 1.55]
Spencer 2003	145	165	36	53	8.0%	1.29 [1.07 , 1.57]
Takahashi 2011	117	143	76	141	9.4%	1.52 [1.28 , 1.80]
Weisler 2009	56	68	43	73	6.7%	1.40 [1.12 , 1.74]
Subtotal (95% CI)		**2325**		**1220**	**100.0%**	**1.32 [1.23 , 1.41]**
Total events:	1775		702			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 17.38$, df = 11 (P = 0.10); $I^2 = 37\%$						
Test for overall effect: Z = 8.09 (P < 0.00001)						
6.8.2 Public with industry-involvement						
Compas 2007 CM	197	205	184	209	62.9%	1.09 [1.03 , 1.16]
Winhusen 2005	122	127	112	128	37.1%	1.10 [1.02 , 1.18]
Subtotal (95% CI)		**332**		**337**	**100.0%**	**1.09 [1.05 , 1.14]**
Total events:	319		296			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.01$, df = 1 (P = 0.90); $I^2 = 0\%$						
Test for overall effect: Z = 3.88 (P = 0.0001)						
Test for subgroup differences: $Chi^2 = 20.58$, df = 1 (P < 0.00001), $I^2 = 95.1\%$						



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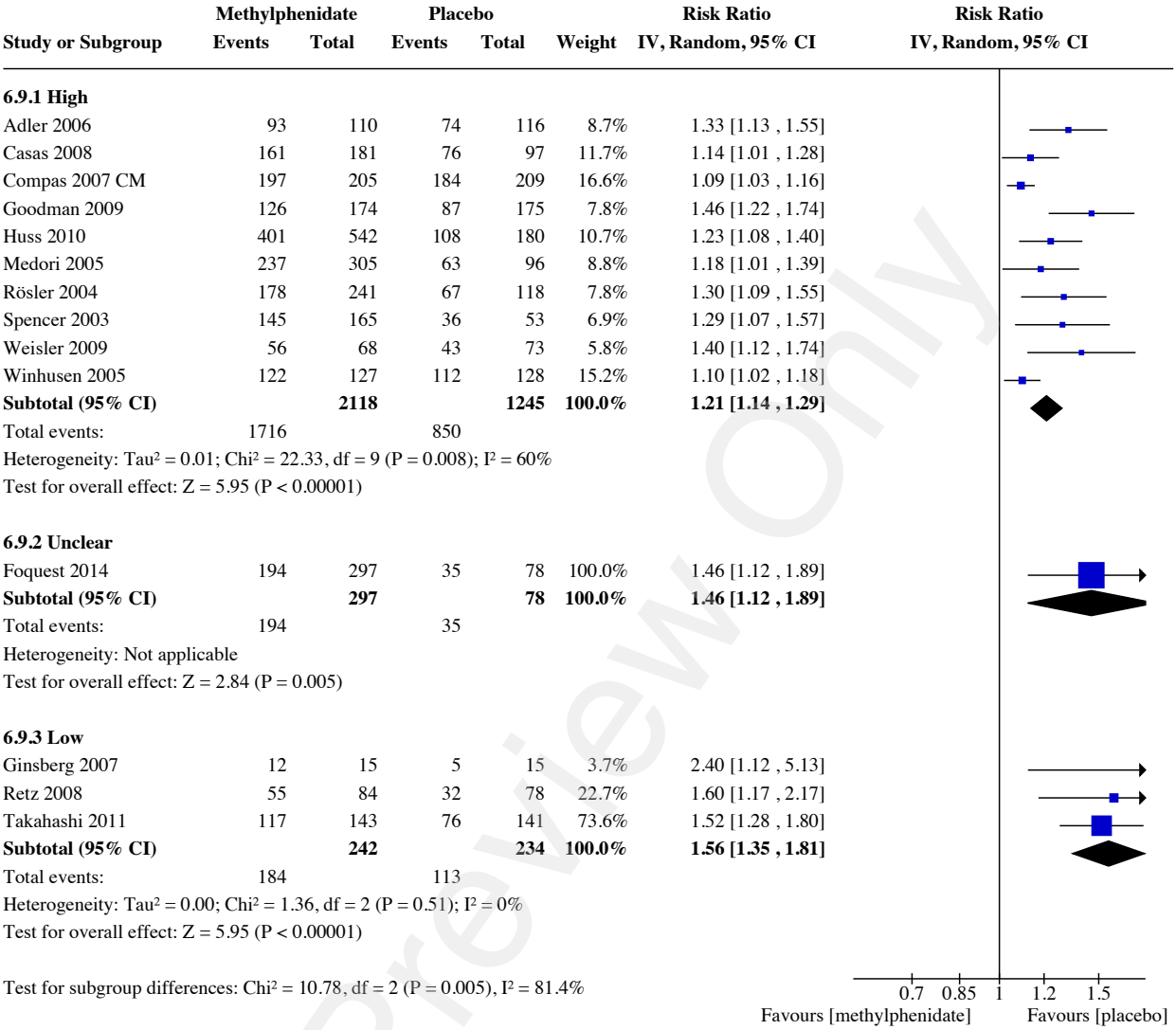
Analysis 6.9. Comparison 6: Extended-release methylphenidate versus placebo: Subgroup and sensitivity, Outcome 9: Proportion experiencing any adverse event: Dropout rates (sensitivity)



Study or Subgroup	Methylphenidate Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
6.9.1 High						
Adler 2006	93	110	74	116	8.7%	1.33 [1.13 , 1.55]
Casas 2008	161	181	76	97	11.7%	1.14 [1.01 , 1.28]
Compas 2007 CM	197	205	184	209	16.6%	1.09 [1.03 , 1.16]
Goodman 2009	126	174	87	175	7.8%	1.46 [1.22 , 1.74]
Huss 2010	401	542	108	180	10.7%	1.23 [1.08 , 1.40]
Medori 2005	237	305	63	96	8.8%	1.18 [1.01 , 1.39]
Rösler 2004	178	241	67	118	7.8%	1.30 [1.09 , 1.55]
Spencer 2003	145	165	36	53	6.9%	1.29 [1.07 , 1.57]
Weisler 2009	56	68	43	73	5.8%	1.40 [1.12 , 1.74]
Winhusen 2005	122	127	112	128	15.2%	1.10 [1.02 , 1.18]
Subtotal (95% CI)		**2118**		**1245**	**100.0%**	**1.21 [1.14 , 1.29]**
Total events:	1716		850			
Heterogeneity: Tau² = 0.01; Chi² = 22.33, df = 9 (P = 0.008); I² = 60%						
Test for overall effect: Z = 5.95 (P < 0.00001)						
6.9.2 Unclear						
Foquest 2014	194	297	35	78	100.0%	1.46 [1.12 , 1.89]
Subtotal (95% CI)		**297**		**78**	**100.0%**	**1.46 [1.12 , 1.89]**
Total events:	194		35			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.84 (P = 0.005)						
6.9.3 Low						
Ginsberg 2007	12	15	5	15	3.7%	2.40 [1.12 , 5.13]
Retz 2008	55	84	32	78	22.7%	1.60 [1.17 , 2.17]
Takahashi 2011	117	143	76	141	73.6%	1.52 [1.28 , 1.80]
Subtotal (95% CI)		**242**		**234**	**100.0%**	**1.56 [1.35 , 1.81]**
Total events:	184		113			
Heterogeneity: Tau² = 0.00; Chi² = 1.36, df = 2 (P = 0.51); I² = 0%						
Test for overall effect: Z = 5.95 (P < 0.00001)						
Test for subgroup differences: Chi² = 10.78, df = 2 (P = 0.005), I² = 81.4%						

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APPENDICES

Appendix 1. eMethods

Minimum duration

We did not define a minimum trial duration as inclusion criteria. However we did not include single-dose studies. Many single-dose experiments have been conducted in laboratory settings where the participants are tested with for instance cognitive tests or in driving simulators.

Trials with more than one phase

Some included trials (e.g. Biederman 2003, Medori 2005, Huss 2010) consisted of several 'phases' with re-randomisation of the participants depending on their clinical response. We included only the first phase of such trials to avoid participant-level unit-of-analysis errors. Additionally, there are several methodological problems related to such study designs that limit their generalisability. The blinding would be difficult to maintain, there would be a risk of exposing those participants re-randomised to placebo to withdrawal effects, and the trial design would favour those who tolerate the drug, which is responder selection ("enriched design").

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Search strategy for other resources

Drug regulatory agencies

We included drug regulatory documents that contained data from clinical trials according to our inclusion criteria. We did not include regulatory documents related to generic drugs or applications that included pharmacokinetic studies or studies in healthy adults only.

We searched 12 drug regulatory agency databases (eTable 1). EMA has not centrally approved any methylphenidate formulations, so we also searched the Heads of Medicines Agency's registry of approved drugs to identify which National Competent Authorities that have approved the drugs in Europe. HMA's MR Index is a European database of approved pharmaceutical drugs in the European Union across the different National Competent Authorities. We acknowledged that the MR Index is not exhaustive and we also hand searched all known European databases of regulatory documents. See overview in eTable 1. We describe each search strategy and detailed results in the Excel datafile (see data sharing statement).

General approach for searching the databases

We searched all databases with the keywords "methylphenidate" and all known approved formulations for use in adults (Concerta, Medikinet, Focalin, Ritalin LA/XL, Ritalin SR, Foquest, Adhansia) or formulations we knew had been tested in adults (Biphentin).

Head of Medicines Agency MR Index, TGA, Health Canada, MEB, PKMD, ANSM, HPRA, and Swissmedic

We used the key word "methylphenidate" and all known trade names for formulations approved for use in adults.

FDA

We used the keyword "methylphenidate". We assessed the clinical reviews to decide whether a Drug Approval Package contained relevant clinical data.

EMA

We searched the database using the tag 'PAR' and the keywords "methylphenidate" and all known trade names.

Medicines and Healthcare products Regulatory Agency (MHRA)

We used the keyword "methylphenidate" and all known trade names with the tag "PAR". We did not assess Patient Information Leaflets or Summary of Product Characteristics.

BfArM

We searched the Arzneimittel-Informationssystem, chose the [Fachkreise] option, and searched for "methylphenidate" as [Stoffnahme]. We did not search for individual trade names.

Clinical trial registries

We searched the clinical trial registries as described in the protocol. Apart from the systematic search, we hand searched and cross-referenced all included studies.

Pharmaceutical companies

We searched the websites and clinical trial databases of the companies that market extended-release methylphenidate formulations approved for use in adults: Novartis (Ritalin LA, Ritalin SR and Focalin), Janssen (Concerta), Medice (Medikinet) and Purdue (Foquest/Adhansia).

Novartis

Clinical Trial Results Database, available at https://www.novctrd.com. We used the keyword "ADHD".

Yale Open Access Database (YODA)

The YODA database (https://yoda.yale.edu/) contains clinical trial results from Johnson & Johnson sponsored trials. Janssen is part of the cooperation. We assessed the trials with the tag "methylphenidate". You may also request clinical study reports from the YODA database. We did not do this for the current version of review. It might be relevant for future updates.

Medice

We searched Medice's website, https://www.medice.de/the-company, but they do not seem to have any publicly available database of clinical trial data. We contacted the company's medical director but our request to access data was declined, see also the discussion.

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Purdue

Purdue has a website dedicated to sharing clinical trial results, https://www.purduepharma.com/healthcare-professionals/clinical-trials/. The data is not publicly available and you have to file a formal request to get access. We decided to not request access to data for this version of the review. It might be relevant for a future update.

Author correspondence

We contacted the corresponding authors for each included trial. We wrote all authors or contact persons for a maximum of three times. If we did not receive an answer the first time we searched Google to identify other relevant email addresses. Some authors were approached already at the protocol stage.

Other methodological issues

Concomitant pharmacological therapy

In most of the included trials participants were allowed (to various degrees) to continue psychopharmacological treatments, such as antidepressants, anxiolytics and similar. How these pharmacological agents affected the reported outcomes is unknown. We would likely need detailed information on an individual participant level to make reliable subgroup analyses based on treatment status. We decided to not go into detail with this question in the current review, but it seems to be an important research questions that needs to be addressed provided there is sufficiently granulated data.

Adverse event data extraction

In some trial reports, two or more events were reported related to the same type of event. For insomnia, if two or more types of insomnia events (e.g. initial and middle insomnia) were reported, we preferred 'initial insomnia'. For sexual dysfunction, we chose those events that seemed to describe more general problems related to sexual function.

Appendix 2. Ovid MEDLINE search strategy

1 "attention deficit and disruptive behavior disorders"/
2 attention deficit disorder with hyperactivity/
3 conduct disorder/
4 ADHD.tw,kf.
5 ADHS.tw,kf.
6 ADDH.tw,kf.
7 ("AD/HD" or hkd).tw,kf.
8 TDAH.tw,kf.
9 ((attention$ or behav$) adj3 (defic$ or dysfunc$ or disorder$)).tw,kf.
10 ((disrupt$ adj3 disorder$) or (disrupt$ adj3 behav$) or (defian$ adj3 disorder$) or (defian$ adj3 behav$)).tw,kf.
11 (impulsiv$ or inattentiv$ or inattention$).tw,kf.
12 hyperkinesis/
13 (hyperkin$ or hyper-kin$).tw,kf.
14 (minimal adj3 brain adj3 (disorder$ or dysfunct$ or damage$)).tw,kf.
15 (hyperactiv$ or hyper-activ$).tw,kf.
16 or/1-15
17 exp Methylphenidate/
18 Adaphen$.mp.
19 Aptensio$.mp.
20 Aradix$.mp.
21 Attenade$.mp.
22 Biphentin$.mp.
23 Calocain$.mp.
24 Centedrin$.mp.
25 Concerta$.mp.
26 Conmet$.mp.
27 Daytrana$.mp.
28 Dexmethylphenidat$.mp.
29 Difumenil$.mp.
30 D-methylphenidat$.mp.
31 Equasym$.mp.
32 Fenilidato$.mp.
33 Focalin$.mp.
34 Matoride$.mp.

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35 Medicebran$.mp.
36 Medikid$.mp.
37 Medikinet$.mp.
38 Meridil$.mp.
39 Metadate$.mp.
40 (Methylphenidylacetat$ or methyl phenidylacetat$).mp.
41 Methylofenidan$.mp.
42 Methylin$.mp.
43 Methypatch.mp.
44 methylphenidat$.mp.
45 Metilfenidato$.mp.
46 Novo-Methylphenidat$.mp.
47 Phenidylate.mp.
48 (Phenidyl hydrochlorid$ or Phenidylhydrochlorid$).mp.
49 Quillivant$.mp.
50 Ritcher Works.mp.
51 Riphenidat$.mp.
52 Ritalin$.mp.
53 Ritrocel$.mp.
54 Rubifen$.mp.
55 Tsentedrin$.mp.
56 or/17-54
57 16 and 56
58 randomized controlled trial.pt.
59 controlled clinical trial.pt.
60 randomized.ab.
61 placebo.ab.
62 clinical trials as topic.sh.
63 randomly.ab.
64 trial.ti.
65 or/58-64
66 exp animals/ not humans.sh.
67 65 not 66
68 57 and 67

Appendix 3. eResults

Search results

The PRISMA flowchart was generated with Covidence. The results from EUCTR and ISRCTN could not be imported directly into Covidence and were added manually. We also summarise the manual search of other resources. The individual resources are detailed in the supplement.

EUCTR/ISRCTN flowchart:

25 records + 2 records (from updated search)

= 27 records for screening

2 records excluded by title

= 25 record for full-text eligibility

20 excluded (9 wrong study design, 6, doublets, 5 wrong intervention)

Total included = 5 records

Manuel search of other resources and cross-referencing:

Drug regulatory databases = 19 records

FDA = 3

TGA = 2

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Canada Health = 2

MHRA = 2

MEB = 1

BfArM = 9

YODA = 6 records

Novartis database = 3 records

Author correspondence = 5 records (Compas 2007 CM (1), Weisler 2009 (1), Winhusen 2005 (1), Ginsberg 2007 (2))

Cross-references = 22

EUCTR entries = 3 records

ClinicalTrials.gov entries = 7 records

Published reports = 10 records (Levin 1998a (1), Compas 2007 CM (4), Huss 2010 (4), Ginsberg 2007 (1))

NiH Reporter = 1 record

Yearly report = 1 record

Total included = 55 records

Drug regulatory databases

See an overview of all included documents in eTable 2.

FDA

Our search returned 20 hits and we included 3 Drug Approval Packages.

TGA

There were no hits in the database of Public Assessment Reports. There were 13 hits in the Register of Traded Goods and we included two Prescribing Information documents.

Health Canada

Our searches in the Summary Decision database and Clinical Study Report database gave 0 hits. Our search in the Drug Product database gave 73 hits, and we included two Product Monographs.

EMA

There were no relevant hits. No extended-release methylphenidate formulation has been centrally approved by the EMA.

MHRA

There were 35 hits with the tag "PAR" searching for "methylphenidate" and we included two Public Assessment Reports. Searching for the individual trade names did not yield further records.

MEB

There were 0 hits with "methylphenidate" and between four and 17 hits with the individual trade names. We included one Public Assessment Report.

BfArM

There were 100 hits searching for "methylphenidate". We included eight documents; Medikinet's Public Assessment Report Summary, two trial synopses (related to Medikinet), four clinical study report synopses (of which two were about extension phases of included studies), and one trial report related to the Compas 2007 study. We were not able to identify the German Public Assessment Report Summary in German, which we were aware of from the Arznei-Telegramm (https://www.arznei-telegramm.de/html/2011_10/1110085_01.html). We included this as a cross-reference (https://portal.dimdi.de/amispb/doc/2011/07/25/2163890/OBFMBD5B836E01CC4AAA.rtf).

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PMDA, ANSM, SwissMedic, and HPRA

There were no hits in the first three databases, and in HPRA there were only Summary of Product characteristics and Patient Leaflets, which we did not assess.

Clinical trial registries

We found 19 trials in ClinicalTrials.gov (eTable 3), nine trials in EU Clinical Trial Register (eTable 4), and four trials ISRCTN (eTable 5). Nine trials were registered in two registries. Ten of these records were found via cross-referencing.

Company data

We found documents related to nine trials. Two documents were about extension phases. See eTable 6. Two of our requests to access data were declined by YODA. Weisler 2009 was a Janssen sponsored trial trial, which compared bavisant, a histamine antagonist, with placebo, OROS methylphenidate and atomoxetine. Our request was declined because bavisant has been out-licensed. Chronis-Tuscano 2004 lists McNeil as sponsor in the published report, and as collaborator and sponsor in the CT.gov entry. We were not granted access to data with the argument that Johnson & Johnson is not the data holder.

Author correspondence

We contacted 22 authors/contact persons corresponding to 24 trials (eTable 7). The Foquest RCT 2014 trial has not been published and therefore no assigned first author.

Nine corresponding authors did not reply. We corresponded with seven authors but got no additional data for various reasons, and we obtained five additional records; Ginsberg (two records), Weisler 2009 (one), Winhusen 2005 (one), and Compas 2007 (one).

Subgroup and sensitivity analyses

We analysed two outcomes, 'overall dropout rates' and 'proportion of participants experiencing any adverse events'. We were unable to do the planned sensitivity analysis based on the risk of bias assessment as all trials were rated high risk.

For 'overall dropout rate', we did four subgroup analyses. We did not do the analysis based on dropout rates, as that would be meaningless.

For 'participants experiencing any adverse event', we did three subgroup analyses and one sensitivity analysis. We did not conduct the 'enriched design analysis', since there were no trials rated low or unclear.

Appendix 4. eTables

eTable 1. Overview of regulatory databases

Regulatory agency	Database of	Link
Heads of Medicines Agency	Overview of approved drugs in the EU	http://mri.cts-mrp.eu/Human/
FDA	Drug Approval Packages	https://www.accessdata.fda.gov/scripts/cder/daf/
TGA	Public Assessment Reports	https://www.tga.gov.au/ws-auspar-index
TGA	Prescribing Information	https://www.tga.gov.au/artg
Health Canada	Clinical Study Reports	https://clinical-information.canada.ca/search/ci-rc
Health Canada	Summary Basis of Decision Letters	https://hpr-rps.hres.ca/reg-content/summary-basis-decision.php
Health Canada	Drug Product Monographs	https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
EMA	Public Assessment Reports	https://www.ema.europa.eu/en/medicines

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(Continued)

MHRA (UK)	Public Assessment Reports, SmPC, PIL	https://products.mhra.gov.uk/
BfArM (DE)	Public Assessment Reports, CSR synopses	PharmNet.bund.de
MEB (NL)	Public Assessment Reports, CSR synopses	https://www.geneesmiddeleninformatiebank.nl/en
PMDA (JN)	Public Assessment Reports	https://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0001.html
ANSM (FR)	Public Assessment Reports	https://www.ansm.sante.fr/Mediatheque/Publications/Rapports-Syntheses-Rapports-publics-d-evaluation
HPRA (IE)	Public Assessment Reports, SmPC, PIL	http://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine
SwissMedic	Public Assessment Reports	https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/authorisations/swisspar.html

eTable 1 legend. Abbreviations: SmPC= Summary of Product Characteristic. PIL= Patient Information Leaflet.

eTable 2. Included drug regulatory documents

Regulatory agency	Document ID	Formulation (trade name)	Clinical trials	Document type
FDA	NDA 21802	Dex-methylphenidate (Focalin XR)	Spencer 2003	Drug Approval Package
FDA	NDA 21121 – supplement 17	OROS-methylphenidate (Concerta)	Medori 2005, Adler 2006	Drug Approval Package
FDA	NDA 212038	Controlled-release methylphenidate (Adhansia)	Foquest 2014	Drug Approval Package
TGA	ARTG 93862-4	OROS- methylpenidate (Concerta)	Medori 2005, Adler 2006, Casas 2008 [a]	Prescribing Information
TGA	ARTG 82957-9	Extended-release methylphenidate (Ritalin LA)	Huss 2010	Prescribing Information
Health Canada	Submission 208669	OROS-methylphenidate (Concerta)	Medori 2005	Drug Product Monograph
Health Canada	Submission 187330	Controlled-release methylphenidate (FOQUEST)	Foquest 2014	Drug Product Monograph
MHRA	PL 00242/0400	OROS-methylphenidate (Concerta)	Medori 2005, Adler 2006, Casas 2008	Public Assessment Report
MHRA	PL 00101/0973-0977	Long-acting methylphenidate	Huss 2010	Public Assessment Report

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		(Ritalin XL)		
MEB	116377, 116379-116382	Long-acting methylphenidate (Ritalin LA/XL)	Huss 2010	Public assessment report
BfArM	DE/H/2222/001-003/DC, DE/H/2222/001-005/DC	Extended-release MPH (Medikinet)	Rösler 2004, Retz 2008	Public Assessment Report Summary (in English)
BfArM	No individual ID	ER methylphenidate (Medikinet)	Rösler 2004	Clinical trial synopsis
BfArM	No individuel ID	Extended-release MPH (Medikinet)	Retz 2008	Clinical trial synopsis [b]
BfArM	2005-004037-18	OROS-methylphenidate (Concerta)	Medori 2005 (extension phase)	CSR synopsis [c]
BfArM	2007-002111-82	OROS- methylphenidate (Concerta)	Casas 2008	CSR synopsis [d]
BfArM	2006-000222-31	ER – methylphenidate (Medikinet)	Compas 2007 CM	Summary results report
BfArM	2010-021533-31	LA- methylphenidate (Ritalin LA)	Huss 2010	CSR synopsis + clinical trial report data [e]
BfArM	2011-000210-19	Long-acting methylphenidate (Ritalin LA)	Huss 2010 (extension phase)	Clinical trial report [b]

eTable 2 legend. ER = Extended-release. OROS= Osmotic Release Oral System delivery. LA = Long-acting. [a)] Some data from Casas 2008 regarding harms were included, but the trial was not specifically mentioned or referred to. [b)] Almost identical to document from EUCTR. [c)] Almost identical to those from CT.gov, EUCTR, and YODA. D) Almost identical to the one from YODA. [e)] The latter part of the document is the same from EUCTR and Novartis database.

eTable 3. Trials registered on Clinicaltrials.gov

NCT ID	Other trial ID	Data available	Document type
NCT00061087*	Levin 1998a	No	N/A
NCT00136734*	Levin 1998b	No	N/A
NCT00181571*	Biederman 2003	No	N/A
NCT00246220	Medori 2005	Yes	Clinical study report synopsis [1]
NCT00253747	Winhusen 2005	Yes	Data on website
NCT00261872	Combine Substudy 2005	No	No
NCT00307684	Medori 2005 extension	Yes	Clinical Study Report synopsis
NCT00318981*	Chronis-Tuscano 2004	No	No

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NCT00326391	Adler 20006	Yes	Clinical study report synopsis (6 pages)[2]
NCT00482313	Ginsberg 2007	No	No
NCT00619840	Rösler 2004	No	No
NCT00714688	Casas 2008	Yes	Data on website[3]
NCT00730249	Retz 2008	No	No
NCT00880217*	Weisler 2009	No	No
NCT00931398	College Study 2009	No	No
NCT00937040	Goodman 2009	Yes	Data on website
NCT01259492	Huss 2010	Yes	Data on website
NCT01323192*	Takahashi 2011	Yes	Data on website
NCT02139124	Foquest 2014	Yes	Data on website
NCT03481959*	Methacan 2017	No	No

eTable 3 legend. 1) The synopsis is about a German extension phase of the study. The document is different to the ones available from YODA and EUCTR. 2) A different CSR synopsis than the one from YODA. 3) A PDF-file of the data is available from EUCTR. * Identified via cross-referencing.

eTable 4. Trials registered on EU Clinical Trial Register

EUCTR ID	Other trial ID	Data available	Document type
200400073037	Medori 2005	Yes	Clinical study report synopsis (8 pages)[1]
2005-004037-18-DE	Medori 2005 extension	Yes	Clinical study report (9 pages)[2]
2006-000222-31*	Compas 2007	N/A	N/A
2006-002249-35	Konstenius 2007	N/A	N/A
2006-002553-80*	Ginsberg 2009	N/A	N/A
2007-002111-82	Casas 2008	Yes	Data on website [2]
2008-000942-29 *	Retz 2008	Yes	Study synopsis (3 pages)
2010-021533-31	Huss 2010	Yes	Clinical trial report (53 pages)[3]
2011-000210-19	Huss 2010 extension	Yes	Clinical trial report (24 pages)[4]
2015-004271-78	Asherson 2016	N/A	N/A

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2017-000386-77	Methacan 2017	N/A	N/A

eTable 4 legend. 1) Identical to the synopsis from YODA, but different to the synopsis from ct.gov. 2) Identical to the one from ct.gov. 3) The data is a PDF-file of those from clinicaltrials.gov. 4) Identical to the document from the Novartis database. * Identified via cross-referencing.

eTable 5. Trials registered on ISRCTN

ISRCTN ID	Other trial ID	Data available	Document type
ISRCTN81602628	Konstenius 2006	No	N/A
ISRCTN77940178	Konstenius 2007	No	N/A
ISRCTN54096201	Compas 2007	No	N/A
ISRCTN16827947	Asherson 2016	No	N/A

eTable 6. Trials identified in pharmaceutical company databases

Database	Document ID	Relevant trial	Document type
Novartis database	CRIT124D2302	Huss 2010	Clinical trial report [1]
Novartis	CRIT124D2302E1	Huss 2010	Clinical trial report [1]
Novartis database	CRIT124E2302	Spencer 2003	Clinical study report synopsis
YODA	NCT00246220	Medori 2005	Clinical study report synopsis[2]
YODA	NCT00307684	Medori 2005 (extension phase)	Clinical study report synopsis[3]
YODA	NCT00326391	Adler 2006	Clinical study report synopsis*
YODA	NCT00714688	Casas 2008	Clinical study report synopsis
YODA	NCT00937040	Goodman 2009	Clinical study report synopsis *
YODA	NCT01323192	Takahashi 2011	Clinical study report synopsis *

eTable 6 legend. 1) Identical to the document obtained from EUCTR. 2) Identical to the one from EUCTR, but different than the one from ct.gov. 3) Identical to the one from EUCTR, but different than the one from ct.gov. *Made available upon our request.

eTable 7. Overview of author correspondence

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Trial	Corresponding author	Sponsor	Outcome	Categorisation
Levin 2001	Edward Levin	Public	No reply after three emails.	No information
Levin 1998a and 1998b	Frances Levin	Public	No reply after three emails.	No information
Spencer 2003	Thomas Spencer	Novartis	No reply after three emails.	No information
Chronis-Tuscano 2004	Andrea Chronis-Tuscano	Public	No reply after three emails.	No information
Rösler 2004	Michael Rösler	Medice	No reply after three emails.	No information
Retz 2006	Wolfgang Retz	Medice	No reply after three emails.	No information
Takahashi 2011	Nagahide Takahashi	Janssen	No reply after three emails.	No information
Methacan 2017	Elodie Soler	Public	No reply after three emails.	No information
Medori 2005	Rossella Medori	Janssen	No reply after three emails.	No information
Adler 2006	Lenard Adler	Janssen	"You need to contact the study sponsor"	Response, no information
Biederman 2003	Joseph Biederman	Janssen	"Sorry. The sponsor has the data."	Response, no information
Casas 2008	Miguel Casas	Janssen	"We have not the raw data as it was a Janssen's study."	Response, no information
Huss 2010	Michael Huss	Novartis	First correspondence: Replied to our first email. Did not reply to our second email where we specified the data we were interested in. Second correspondence: "Thank you for contacting me on this behalf. However, I was a bit irritated since we did not have OROS-methlyphenidate but MPH-LA in our study" [In the email, we had written OROS-MPH and not MPH LA]	Response, no information

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Asherson 2016	Philip Asherson	Public	Replied to our first email. Did not reply when we asked for the protocol or available data.	Response, no information
Combine Substudy 2005	Raymond Anton	Public	Raymod Anton (contact) referred us to NIH database, but informed us there would be no information of interest. Contacted the data manager, Raye Litten about the content of the data. No reply after three emails	Response, no information
Konstenius 2006 and 2007	Maija Konstenius	Public	Replied to our first email. Did not respond to our second email where we specified our request.	Response, no information
College Study	Oscar Bukstein	Janssen	Reply: "I apologize; the project funding was withdrawn before we got started. I forgot to take this off clinicaltrials.gov Oscar Bukstein" Our response: "Thank you indeed for the quick reply. Can you tell me why the funding was withdrawn, it seemed like a very important study?" Reply to our question: "We thought so too. Investigator-initiated pharma sponsored study. The bosses thought it was too close to end of patent."	Response, additional information
Ginsberg 2007	Ylva Ginsberg	Public	Sent PhD thesis + one published article	Response, additional information
Weisler 2009	Ella Daly	Janssen	Sent conference proceeding. Referred to YODA database for further information	Response, additional information
Winhusen 2005	Theresa Winhusen	Public with industry-involvement	Sent protocol and link to trial database	Response, additional information
Compas 2007	Alexandra Philipsen	Public with industry-involvement	Sent documents related to adverse events and serious adverse events and referred to BfArM's website for trial report.	Response, additional information
Goodman 2009	H Lynn Starr (medical director, Janssen)	Janssen	Contacted by Mikael Själin, Therapeutic Area Head, that we should request the data at YODA	Response, additional information

eTable 8. Specification of serious adverse events

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	Methylphenidate			Placebo		
Study	**N**	**No. SAEs**	**Type of event(s)**	**N**	**No. SAEs**	**Type of event(s)**
Biederman 2003	109	0	None	114	0	None
Spencer 2003 [a]	165	2 events in 2 participants	Ulcerative colitis and hypovolemic shock, high fever and loss of consciousness	53	0	None
Medori 2005 [b]	305	4 events in 4 participants	Cerebrovascular accident, anxiety disorder, migraine attack, depressive disorder	96	0	None
Winhusen 2005	127	2	Car accident, worsening of depression leading to hospitalisation	128	0	None
Adler 2006[c]	110	0	None	116	0	None
Compas 2007 CM[i]	205	19 events in 15 participants	Depression (1), suicidal ideation (1), aggression (1), tension (1), somnambulism (1), alcohol poisoning (1), appendix disorder (1), ocular hypertension (1), retinal detachment (1), cholecystectomy (1), rehabilitation therapy (1), adenomyosis (1), haemorrhagic ovarian cyst (1), transient ischaemic attack (1), pneumonia (1), pregnancy (2), chest pain (1), tachycardia (1).	209	12 events in 9 participants	Depression (1), suicidal ideation (1), road traffic accident (2), epicondylitis (1), fall (1), abdominal discomfort (1), gastrointestinal pain (1), ovarian cyst (1), syncope (1), salpingitis (1), vertigo (1), arthroscopy (1).
Ginsberg 2007	15	0	None	15	0	None
Konstenius 2007[e]	27	0	None	Not reported	Not reported	Not reported
Retz 2008	84	1	Rupture of the acromioclavicular joint	78	2	Appendicitis, postoperative pain
Casas 2008[f]	181	7 events in 5 par-	Abdominal pain + nausea, ruptured ovarian cyst, suicidal ideation and subsequent suicide attempt, concussion, inter-vertebral disc protrusion (1 each)	97	2 events in 2 par-	Cholecystitis (1), joint injury (1)

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		tici-pants			tici-pants	
Good-man 2009	174	0	None	175	1 event in 1 par-tici-pant	Suicidal ideation
Weisler 2009 [d]	68	1	Convulsion	73	1	Pericarditis
Huss 2010[g]	542	4 events in 4 par-tici-pants	Goiter, infected bites, loss of consciousness, ovarian cyst rupture	180	6 events in 2 par-tici-pants	Sudden hearing loss and vertigo, eye infec-tion, syncope, agita-tion and depression
Taka-hashi 2011	143	2	Psychotic disorder, tension pneumothorax	141	0	None
Fo-quest 2014[h]	297	16 events in 12 par-tici-pants	Diarrhoea (1), feeling jittery (1), cellulitis (1), muscle strain (1), osteoarthritis (1), uterine cancer (1), headache (1), anxiety (1), emotional disorder (1), insomnia (3), mood altered (1), psychotic disorder (1), calculus urinary (1), nephrolithiasis (1).	78	2 events in 2 par-tici-pants	Headache (2)

eTable 8 legend. The 15 trials reporting serious adverse events for at least one group. [a)] Reported in FDA Medical Review, p. 19. The three other events occurred in extension phase. [b)] "Aggression and delusion of reference" was not listed as a SAE. [c)] "Abnormal thinking" was not listed as a SAE. [d)] The pericarditis event in the placebo group occurred after study completion, but not described when exactly. In Huss 2010, the aneurism event was not included since it occurred after study completion. [e)] Reported in conference proceeding, but not for placebo group. [f)] Data according to ClinicalTrials.gov. [g)] Death (in methylphenidate group) due to aortic dissection rupture 21 days after study completion was not reported as a SAE. [h)] There were important differences between reported SAEs in Health Canada's Product Information, FDA's Medical Review and on ClinicalTrials.gov. We used the ClinialTrials.gov results. [i)] Reported for the two methylphenidate and placebo groups together at 52 weeks follow-up.

eTable 9. Serious adverse events or severe psychiatric adverse events (table 1 of 3)

	Serious psychiatric adverse events and severe psychiatric adverse events		
Study	**MPH**	**Placebo**	**Comments**
Levin 1998a	Not reported	Not reported	Adverse effects were collected ac-cording to severity (mild/moder-ate/severe), but they were not re-ported in the paper.
Levin 1998b	Not reported	Not reported	Adverse effects were collected ac-cording to severity (mild/moder-

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			ate/severe), but they were not reported in the paper.
Levin 2001	Not reported	Not reported	
Biederman 2003	No SAEs. Severe adverse events not described	No SAEs. Severe adverse events not described	
Spencer 2003	0 SAEs. Overall rate of "severe adverse events" of 8.5 %; insomnia (2 participants).	0 SAEs. Rate of "severe adverse events" of 5.7 %. Events not specified for placebo participants.	Only "severe adverse events" occuring in more than one participant described (Spencer 2007)
Chronis-Tuscano 2004	Not reported	Not reported	
Rösler 2004	Not reported	Not reported	Akathisia and dyskinesia mentioned in the text as "neurological abnormalities", but not detailed.
Medori 2005	2 SAEs: depression and anxiety. Three events were listed as "severe" but without number of participants experiencing them; thinking abnormal, delusion of reference, abnormal behaviour.	0 SAEs, "severe adverse events" not systematically reported.	Not reported systematically, those events only mentioned sporadically in MHRA PAR p. 63.
Winhusen 2005	1 SAE (worsening of depression). Severe adverse events not described	No SAEs. Severe adverse not described	
Adler 2006	0 SAEs. 4 "severe" adverse events: Abnormal thinking (1), irritability (1), anxiety (1), initial insomnia (1)	0 SAEs. 2 "severe adverse events": somnolence (1) and affect lability (1).	Reported in Adler, p. 244.
Konstenius 2006	SAEs not reported. No severe adverse events.	SAEs not reported. No severe adverse events.	"Reported Aes were mild and reversible", so we expect that no severe events occurred.
Compas 2007	5 SAEs: Depression (1), suicidal ideation (1), aggression (1), tension (1), somnambulism (1). Severe adverse events not described.	2 SAEs: Depression (1), suicidal ideation (1. Severe adverse events not described.	Reported in document sent by corresponding author
Ginsberg 2007	No SAEs. Severe adverse events not described.	No SAEs. Severe adverse events not described. Intrusive thoughts (1), but event not described further	Intrusive thoughts, Ginsberg 2013 report, p 24. "The severity of AEs was usually rated as mild to moderate and not a reason for discontinuation" (Thesis, p. 53)
Konstenius 2007	No SAEs. No reporting of severe adverse events.	SAEs not reported. No reporting of severe adverse events. Hearing voices (1), but this event is not described further.	
Casas 2008	2 SAEs in one participant: 1 suicide ideation and 1 suicide attempt. Severe adverse events not specified.	No SAEs of interest. Severe adverse events not spcified.	Rate of severe adverse events reported in CSR synopsis but events not specified

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Retz 2008	No relevant SAEs. "No severe adverse events related to study medication".	No relevant SAEs. "No severe adverse events related to study medication".	Retz 2012, p. 57.
Goodman 2009	0 SAEs. 3 participants with "severe adverse events": anxiety (1), restlessness (1), and nervousness and jitter (1).	1 SAE: suicidal ideation. 1 "severe adverse event": insomnia.	Severe adverse events reported in Goodman 2017, p. 111.
Weisler 2009	No SAEs. Severe adverse events not described. Suicidal ideation (1), but event not described further	No SAEs. Severe adverse events not described. Suicidal ideation (1), but event not described further	The suicidal events were captured using the Columbia Suicide Severity Rating Scale.
Huss 2010	0 SAEs. Severe adverse events not described.	2 SAEs: depression and agitation (unclear if one or two participants). Severe adverse events not described.	
Takahashi 2011	1 SAE (psychotic disorder). 9 answered yes to questions regarding suicidal ideations (6 in CSR synopsis). Severe adverse events not described.	0 SAEs. 9 participants answered yes to questions regarding suicidal ideation (2,9 %, corresponding to 4 participants in CSR synopsis). Severe adverse events not described.	The suicidal events were captured using the Columbia Suicide Severity Rating Scale (Like in Weisler 2012)
Foquest 2014	8 SAEs: Anxiety (1), emotional disorder (1), insomnia (3), mood altered (1), psychotic disorder (1), feeling jittery (1). Severe adverse events not described.	0 SAEs. Severe adverse events not described.	Data used from CT.gov. Note that in FDA's Clinical Review, the SAEs are called "significant adverse events" (p. 35 of 57).

eTable 10. Dose reductions due to psychiatric adverse events (table 2 of 3)

	Dose reductions (due to psychiatric adverse events)		
Study	**MPH**	**Placebo**	**Comments**
Levin 1998a	3 participants but the adverse events were not reported	0	Reasons for dose reduction not described
Levin 1998b	3 participants (insomnia, depressed, clenched jaws)	1 participant (sedation)	
Levin 2001	Fixed dose	Fixed dose	
Biederman 2003	Not reported	Not reported	
Spencer 2003	Fixed dose	Fixed dose	
Chronis-Tuscano 2004	Not reported	Not reported	
Rösler 2004	Not reported	Not reported	
Medori 2005	Fixed dose	Fixed dose	

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Winhusen 2005	Not reported	Not reported	
Adler 2006	Anxiety (3)	Not reported	Only events leading to dose reduction in 2 % or more were reported. Adler 2009, p. 244.
Konstenius 2006	Not reported	Not reported	Nervousness (1), but not described if it occurred in MPH or placebo arm.
Compas 2007	Not reported	Not reported	
Ginsberg 2007	Fixed dose	Fixed dose	
Konstenius 2007	Feeling edgy (1)	Suicidal ideation (1)	The event in the placebo group led to "study medication discontinuation"
Casas 2008	Fixed dose	Fixed dose	
Retz 2008	19 total dose reductions (reasons for reduction not described)	2 total dose reductions (reasons for reduction not described)	Retz 2012, p. 53.
Goodman 2009	Not reported	Not reported	
Weisler 2009	Not allowed according to protocol	Not allowed according to potocol	
Huss 2010	Fixed dose	Fixed dose	
Takahashi 2011	Not reported	Not reported	
Foquest 2014	Fixed dose	Fixed dose	

eTable 11. Dropouts due to psychiatric adverse events (table 3 of 3)

	Dropouts (due to psychiatric adverse events)		
Study	**MPH**	**Placebo**	**Comments**
Levin 1998a	Psychomotor agitation (1)	0	We did not count the fatigue event in the placebo group as psychiatric
Levin 1998b	Persistent insomnia (1) + 2 participants were "removed from the protocol because of worsening of pre-existing mood lability [and] anxiety"	3 participants were "removed from the protocol because of worsening of pre-existing depression".	Unsure what the removal from the protocol means. Described in Levin 2007, p. 22 (3.1. participant flow). In the flowchart, respectively 3 (MPH) and 2 (placebo) participants listed as dropout due to "psychiatric", but not described further.
Levin 2001	Not reported	Not reported	None

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Biederman 2003	6 AEs leading to drop out: jitteriness (1), irritability (3), depression (1), anxiety (1)	One dropout (irritability) but not described in which trial (IR-MPH or OROS-MPH) in Biederman 2007	Described in Biederman 2007, which reported data from the interim analysis
Spencer 2003	Insomnia (3), jittery (2), anxiety (2)	1 (insomnia)	Only adverse events leading to drop out in more than two participants reported (FDA Labelling). The insomnia event in the placebo group described in Spencer 2007, calculated from 1.9%
Chronis-Tuscano 2004	No dropouts	No dropouts	None
Rösler 2004	Not reported	Not reported	None
Medori 2005	11 participants experiencing 12 events: anxiety (4), irritability (3), nervousness (3), restlessness (2), insomnia (2).	No events	Reasons for dropouts only reported for events experienced by two participants or more. We also included insomnia although it is classified as a nervous system disorder in the table (MHRA PAR p. 59)
Winhusen 2005	No dropouts due to adverse events	No dropouts due to adverse events	None
Adler 2006	5 participants and 7 events: Anxiety (3), agitation, mood altered, panic attack, thinking abnormal (1 each)	3 participants and 3 events: depressed mood (2), depression (1)	FDA Medical Review, p. 103 of 456
Konstenius 2006	Not reported	Not reported	None
Compas 2007	Not reported	Not reported	Only the number of participants who stopped MPH or placebo due to Aes was reported (Philipsen 2015, Fig 1), but unclear if they dropped out of the study. Type of adverse events not reported.
Ginsberg 2007	No dropouts	No dropouts	None
Konstenius 2007	Not reported	Not reported	None
Casas 2008	Insomnia (5)	Not reported	Only the most common reason, insomnia, was reported in Casas 2013, p. 275
Retz 2008	Not reported	Not reported	None
Goodman 2009	2 participants: anxiety (1), anxiety and insomnia (1).	1 participant: suicidal ideation (1=the SAE)	Goodman 2016, p. 107
Weisler 2009	Not reported	Not reported	None

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Huss 2010	47 reported participants: Anxity (9), Agitation (5), depressed mood (5), depression (5), insomnia (5), irritability (4), Restlessness (4), aggression (2), apathy (2), disturbance in attention (2), impulse-control disorder (2), panic attack (2)	4 reported participants: Anxiety (1), agitation (1), depression (1), panic attack (1).	"Adverse event leading to dropout" reporting threshold; 0,4 % in CTR (p. 40) and 2% in publication.
Takahashi 2011	Not reported	Not reported	None
Foquest 2014	Anxiety (2), insomnia (2), affect lability (1), emotional disorder (1), irritability (1)	Irritability (2)	FDA Clinical Review, table 13, p. 35 of 57

Appendix 5. Plot legends

ADHD symptoms self rated *(1.2): Eleven trials reported end point values and four mean change scores. For Levin 1998a and Konstenius 2007 we imputed SD values. For Rösler 2004 and Retz 2008, we calculated SD values based on reported endpoint value and effect size. For Weisler 2009, we extracted data from graph and imputed the missing placebo SD value to be the same as for MPH.*

Quality of life *(1.4): Two trials reported end point values and three trials reported mean change scores. We recalculated the reported Compas 2007 data from percentage of maximum score to a mean value with corresponding confidence intervals. We used the LMCF values rather than completers' data (BfArM submission, table 6).*

Quality of life (QSF mean difference) *(1.5): We recalculated the reported Compas 2007 data from percentage of maximum score to a mean value with corresponding confidence intervals. We used LMCF values rather than completers' data (BfArM submission, table 6).*

ADHD symptoms investigator rated *(1.7): 17 trials reported end point values and three trials reported mean change scores. We calculated SDs for Retz 2008 and Rösler 2004 based on the reported endpoint values and effect sizes. For Levin 1998b, we assumed the reported variation was SEM.*

Systolic blood pressure *(2.2): We imputed SD values for Medori 2005. Biederman 2003 reported interim results only.*

Diastolic blood pressure *(2.3): We imputed SD values for Medori 2005. Biederman 2003 reported interim results only. Konstenius 2007 did not report data from the placebo group, but we noted that the methylphenidate group data were the same before and after treatment, down to the decimal.*

Pulse *(2.4): We imputed SD values for Medori 2005 and Takahashi 2011. Biederman 2003 reported interim results only.*

Weight *(analysis 2.5): We imputed SD values for Spencer 2003 (placebo group), Rösler 2004 and Medori 2005. Biederman 2003 reported interim data only. Casas 2008 reported change data as kg/m2 and was not included.*

Dry mouth *(analysis 2.12): From Biederman 2003 we extracted "muscosal dryness" and from Takahashi 2011 "thirst".*

Palpitations *(analysis 2.15): From Biederman 2003, we extracted "cardiovascular".*

Insomnia *(analysis 2.16): Three trials (Levin 1998b, Biederman 2003, Takahashi 2011) reported 'insomnia', Rösler 2004 reported 'difficulties falling asleep', Ginsberg reported 'insomningsvårigheter', Konsteinus 2007 reported 'sleep problems', and the remaining ten trials reported 'initial insomnia'.*

Sexual dysfunction *(analysis 2.17): Medori 2005, Adler 2006 and Casas 2008 reported 'libido deceased' as a pooled estimate in MHRA's report. Rösler 2004 reported 'reduced libido', Huss 2010 and Weisler 2009 reported 'libido decreased', Foquest RCT 2014 reported 'abnormal orgasm'. Biederman 2003 and Compas 2007 reported 'sexual dysfunction'.*

Depression *(analysis 2.19): Medori 2005, Adler 2006, Casas 2008 was reported as a pooled estimate. Biederman 2003 reported 'sad/down'.*

Agitation *(analysis 2.22): Medori 2005, Adler 2006, Casas 2008 was reported as a pooled estimate.*

Aggression *(analysis 2.23): Medori 2005, Adler 2006, Casas 2008 was reported as a pooled estimate.*

MPH vs. ATX: Self-rated ADHD symptoms *(analysis 3.6): We extracted mean change and confidence intervals from graph (Weisler 2012).*

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Quality of life, medium-term *(analysis 5.7): We recalculated the reported Compas 2007 data from percentage of maximum score to a mean value with corresponding confidence intervals. We used the LMCF values rather than completers' data (BfArM submission, table 6).*

HISTORY

Protocol first published: Issue 11, 2017
Review first published: Issue 7, 2020

CONTRIBUTIONS OF AUTHORS

Data sharing statement

The dataset used for the analyses will be made available in Excel format at the Open Science Framework (*insert link upon publication*).

DECLARATIONS OF INTEREST

Kim Boesen is a PhD student with the Nordic Cochrane Centre.
Asger Sand Paludan-Müller is a PhD student with the Nordic Cochrane Centre.
Peter C Gøtzsche is the Director of the Institute for Scientific Freedom.
Karsten Juhl Jørgensen is acting director of the Nordic Cochrane Centre.

SOURCES OF SUPPORT

Internal sources

- Nordic Cochrane Centre, Denmark

  Supported the review authors: KB, ASP and KJ.

External sources

- None, Other

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Paper 2

Considering the methodological limitations in the evidence base of antidepressants for depression: a reanalysis of a network meta-analysis

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BMJ Open 2019; 9:e024886.

GRADUATE SCHOOL OF HEALTH AND MEDICAL SCIENCES
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1. Declaration by	
Name of PhD student	Kim Boesen
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Name of principal supervisor	Jacob Rosenberg
Title of the PhD thesis	Methodological limitations in psychiatric drug trials with a particular focus on extended-release methylphenidate

2. The declaration applies to the following article	
Title of article	Considering the methodological limitations in the evidence base of antidepressants for depression: a reanalysis of a network meta-analysis
Article status	
Published ☒ Date: 27 June 2019	Accepted for publication ☐ Date:
Manuscript submitted ☐ Date:	Manuscript not submitted ☐
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	BM Open 2019; 9:e024886 . Doi:10.1136/ bmjopen-2018-024886 .

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5. Conducting the analysis of data	C
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7. Writing of the first draft of the manuscript	C
8. Finalisation of the manuscript and submission	C
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	Date	Name	Title	Signature
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6. Signature of the principal supervisor

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 15/7/20
Principal supervisor: Jacob Rosenberg

7. Signature of the PhD student

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
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PhD student: Kim Boesen

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[ii] Please see Ministerial Order on the PhD Programme at the Universities and Certain Higher Artistic Educational Institutions (PhD Order) § 12 (4):

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BMJ Open

Considering the methodological limitations in the evidence base of antidepressants for depression: a reanalysis of a network meta-analysis

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To cite: Munkholm K, Paludan-Müller AS, Boesen K. Considering the methodological limitations in the evidence base of antidepressants for depression: a reanalysis of a network meta-analysis. *BMJ Open* 2019;**9**:e024886. doi:10.1136/bmjopen-2018-024886

► Prepublication history and additional material for this paper are available online. To view, please visit the journal (http://dx.doi.org/10.1136/bmjopen-2018-024886).

Received 19 June 2018
Revised 18 October 2018
Accepted 8 May 2019

Check for updates

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ABSTRACT

Objectives To investigate whether the conclusion of a recent systematic review and network meta-analysis (Cipriani *et al*) that antidepressants are more efficacious than placebo for adult depression was supported by the evidence.

Design Reanalysis of a systematic review, with meta-analyses.

Data sources 522 trials (116 477 participants) as reported in the systematic review by Cipriani *et al* and clinical study reports for 19 of these trials.

Analysis We used the Cochrane Handbook's risk of bias tool and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate the risk of bias and the certainty of evidence, respectively. The impact of several study characteristics and publication status was estimated using pairwise subgroup meta-analyses.

Results Several methodological limitations in the evidence base of antidepressants were either unrecognised or underestimated in the systematic review by Cipriani *et al*. The effect size for antidepressants versus placebo on investigator-rated depression symptom scales was higher in trials with a 'placebo run-in' study design compared with trials without a placebo run-in design (p=0.05). The effect size of antidepressants was higher in published trials compared with unpublished trials (p<0.0001). The outcome data reported by Cipriani *et al* differed from the clinical study reports in 12 (63%) of 19 trials. The certainty of the evidence for the placebo-controlled comparisons should be very low according to GRADE due to a high risk of bias, indirectness of the evidence and publication bias. The mean difference between antidepressants and placebo on the 17-item Hamilton depression rating scale (range 0–52 points) was 1.97 points (95% CI 1.74 to 2.21).

Conclusions The evidence does not support definitive conclusions regarding the benefits of antidepressants for depression in adults. It is unclear whether antidepressants are more efficacious than placebo.

Strengths and limitations of this study

- ► Empirical evidence was provided showing how many biases and methodological limitations in the evidence base for antidepressants for depression affect the apparent effect size for antidepressants.
- ► For the first time, the impact of the 'placebo run-in' study design on the apparent effect size for antidepressants compared with placebo was estimated.
- ► We reported the effect estimate of antidepressants compared with placebo as a mean difference on the investigator-rated Hamilton depression rating scale to provide an outcome measure that can be easily interpreted by patients and clinicians.
- ► When possible, we compared the data reported by Cipriani *et al* on the outcomes of total dropouts and dropouts due to adverse events with the clinical study reports that we have previously obtained from the European Medicines Agency.
- ► Our analyses relied on the data reported in the systematic review by Cipriani *et al* and we did not perform a separate literature search and data extraction; given the methodological limitations we have identified, a reliable assessment would need to be based on clinical study reports and individual patient data.

INTRODUCTION

WHO estimates that 300 million people globally suffer from depression, making depression the leading cause of disability worldwide.[1] In Denmark, 10% of all adults 25 years and older were in treatment with antidepressants in 2016.[2] In the USA, 13% of persons 12 years and older were in treatment in 2014, making antidepressants one of the three most commonly used drug classes.[3] Prescriptions for antidepressants cost the National Health Service in the UK an estimated £267 million in 2016.[4] Research that guides clinical treatment of depression therefore has a potentially important impact on millions of people and on national economies.

The recent network meta-analysis of antidepressants for depression by Cipriani *et al*[5] is the largest meta-analysis of antidepressants to date in terms of included studies and participants. It specifically aimed to inform clinical guidelines, patients, physicians and

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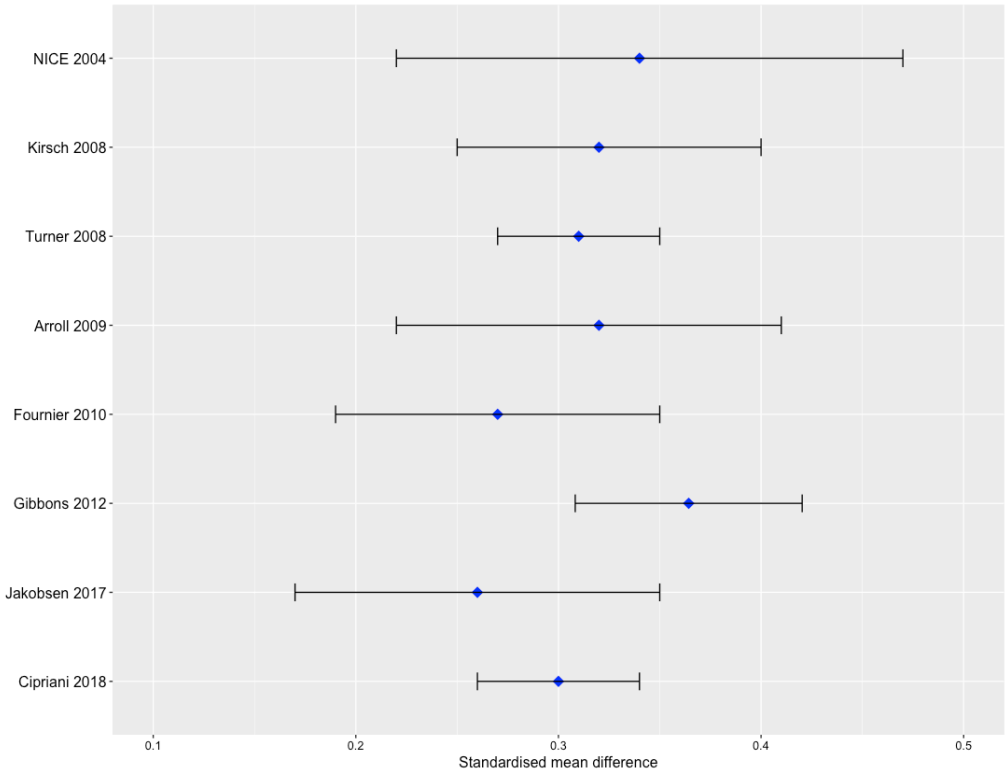

Figure 1 Previous meta-analyses reporting effect sizes for antidepressants versus placebo in adults. Data are reported as standardised mean differences with 95% CIs. NICE 2004[6]: SSRIs. Kirsch 2008[8]: 'new generation' antidepressants. Turner 2008[9]: all antidepressants. Arroll 2009[41]: antidepressants for depression in primary care. Data represent a pooled estimate of tricyclic antidepressants and SSRIs versus placebo, fixed-effects model. Fournier 2010[42]: all antidepressants. Data represent pooled estimate from three groups of severity (mild to moderate, severe, very severe), fixed-effects model. Gibbons 2012[43]: fluoxetine and venlafaxine. Jakobsen 2017[7]: SSRIs. The effect size of mean change scores. Cipriani 2018[5]: all antidepressants. SSRIs, selective serotonin reuptake inhibitors.

policy makers by comparing 21 antidepressants for the treatment of adults with depression. The review's primary outcomes were 'response rate' (defined as the number of participants with at least a 50% reduction on an observer-rated depression scale) and overall dropout rates. The secondary outcomes were depression symptom scores, 'remission rate' (defined as the number of participants with an observer-rated depression score below a certain threshold), and dropouts due to adverse events. Cipriani *et al* found that all 21 antidepressants were more effective than placebo, whereas only two of the drugs had fewer dropouts compared with placebo. Based on these findings, they[5] ranked the antidepressants according to response rate and overall dropout rate and concluded that antidepressants were more efficacious than placebo in adults with major depressive disorder. The improvement in symptom scores they found were very similar to previous meta-analyses (figure 1), some of which have concluded that the benefit of antidepressants is doubtful.[6–9] The review received widespread media coverage, largely citing it as finally putting to rest any doubts regarding the efficacy of antidepressants,[10 11] and the message of antidepressants being effective was strongly conveyed by some of the authors in the press,[10] adding that the benefits outweigh side effects.[11]

There are many methodological limitations in trials of antidepressant agents,[12] of which many have been acknowledged for decades.[13] Research aiming to inform clinical practice on the use of antidepressants for depression must recognise these limitations. We have already addressed some of the limitations in the risk of bias assessment in the Cipriani *et al* review.[14] However, given the potential implications of Cipriani *et al*'s review,[5] we here aimed to provide a more comprehensive assessment. Specifically, we wished to investigate how the methodological limitations in the evidence base were addressed, whether the review's assessment of the risk of bias within the included trials and the evaluation of the certainty of evidence were appropriate and followed the authors' stated methods, and whether the conclusion was supported by the evidence. We furthermore aimed to provide empirical evidence on the impact of these methodological limitations by using the data reported by Cipriani *et al*.[5]

METHODS

Data collection

We extracted the review's risk of bias assessments and descriptive data from the online supplement and

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converted the data to Microsoft Excel format. We downloaded the online dataset[5] and merged the files for our statistical analyses.

We cross-referenced the included trials with the clinical study reports that we previously obtained from the European Medicines Agency in 2010.[15] We compared the outcomes of total dropout rates and dropouts due to adverse events as reported in the clinical study reports with the data reported by Cipriani *et al*.[5]

Statistical analyses

Descriptive analyses were made in Microsoft Excel. We used the statistical software R V.3.4.3 for random-effects meta-analyses based on the inverse variance method and calculated effect sizes as standardised mean differences (SMD) as Hedges' g with corresponding 95% CI. The extent of variation among the intervention effects observed in different studies was calculated as Tau^2 and the percentage of the variability in effect estimates that was due to heterogeneity was calculated as I^2. For the comparisons between antidepressants and placebo on rating scales, we used the Hartung-Knapp-Sidik-Jonkman approach because it results in fewer type I errors than the DerSimonian and Laird approach.[16] We based our analyses on the number of participants from Cipriani *et al*'s 'efficacy' analyses.[5] In studies with more than one drug arm, the total number of participants in the placebo group was split evenly between the active comparisons and the means and SD were unchanged.[17] We did subgroup analyses based on the use of a 'placebo run-in' study design, sponsorship and publication status, according to the trial characteristics published by Cipriani *et al*.[5]

Quality assessments

We evaluated whether Cipriani *et al*'s risk of bias assessments were in accordance with the Cochrane Handbook,[17] as stated by the authors.[5] Where the approach differed we compared the risk of bias assessment by Cipriani *et al*[5] with our reassessment following the Cochrane Handbook.[17] The specific domains (and type of bias) assessed were sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias.[17]

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[18] approach to evaluate the certainty of evidence, which, for systematic reviews, reflects the extent of confidence that an estimate effect is correct. GRADE considers five domains that affect the quality of the evidence: the included trials' internal risk of bias, inconsistency of the included trials' results and large heterogeneity, indirectness of the evidence due to poor external validity, imprecision of the effect estimate and wide CIs, and publication bias.[18]

Patient and public involvement

No patients were involved in the development of the research question, design and implementation of the study, or interpretation of the results.

RESULTS

Risk of bias

Randomisation sequence generation and allocation sequence concealment

Cipriani *et al*[5] judged 426 (82%) and 460 (88%) of the 522 included trials to be of unclear risk of bias with respect to randomisation sequence generation and allocation concealment, respectively. The remaining trials were of low risk of bias. Trials at high or unclear risk of bias within these two domains are likely to report inflated effect estimates, especially of subjective outcomes.[19] Cipriani *et al* did not describe how they assessed the risk of bias in relation to the randomisation sequence generation or the allocation concealment, and we were therefore unable to evaluate if their methods followed those outlined in the Cochrane Handbook.[17]

Blinding of participants, personnel and outcome assessment

Cipriani *et al*[5] did not use the standard Cochrane categorisation of low, unclear or high risk of bias due to a lack of blinding.[17] They categorised instead 513 (98%) studies as 'stated-not tested' in at least one of the three blinding domains, meaning that the trial had stated to be double-blind, but did not test the blinding integrity. While this implied the presence of a blinding issue, their categorisation did not affect the overall risk of bias assessment[5] and it seemed that the stated-not tested domains were counted as 'low risk of bias'. Two of the three trials categorised by Cipriani *et al*[5] to be at low risk of bias in the blinding of participants' domain had tested the blinding integrity (online S1 Appendix). The blinding was likely compromised in both trials. Adverse effects of antidepressants are common and often reveal who receives active medication and who receives placebo in a randomised trial. The degree of unblinding is extensive and leads to inflated effect estimates,[20] and smaller effects have been observed when the trials were better blinded by adding atropine to the placebo.[21] Given these issues, all placebo-controlled trials of antidepressants should arguably be categorised as at least unclear, or perhaps even at high risk of bias.

Incomplete outcome data

Cipriani *et al* rated trials that used an appropriate imputation method as low risk of bias.[5] Trials that used an 'inappropriate' imputation method were rated according to several arbitrary cut-offs: when the dropout rates were unbalanced between the arms, defined as more than a 5% difference for the head-to-head comparisons and a 10% difference for the placebo comparisons, they were rated as high risk of bias. When the dropout rates between the arms were not unbalanced but the total dropout rate was

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>20% they were rated unclear, and if the total dropout rate was <20% they were rated as low risk of bias. This method is not in accordance with the Cochrane Handbook, which emphasises that it is not possible to formulate a simple rule for judging a study to be at low or high risk of attrition bias in that the risk of bias depends on several factors.[17] Further, the authors did not consider the reasons for dropout, although this is also recommended by the Cochrane Handbook.[17]

According to Cipriani *et al*, 121 (23%) trials were at high risk of attrition bias, but we could not replicate these results. The overall attrition rate was >20% in 334 (64%) trials. Using the cut-offs defined by Cipriani *et al*, we found that the dropout rates were unbalanced between the arms in 202 trials (39%) and according to the methods described by Cipriani *et al*[5] they should have been rated as high risk of bias unless an 'appropriate imputation method' was used. Cipriani *et al* characterised the last observation carried forward (LOCF) method as inappropriate,[22] but they did not provide data on the used imputation method in the included trials. We were therefore not able to apply Cipriani *et al*'s categorisations in our reassessment of the attrition bias. Most antidepressant trials use the LOCF imputation method,[23] which may lead to an underestimation of the variability, a falsely low p value and an overestimation of treatment effects.[24]

Selective outcome reporting

Cipriani *et al*[5] judged that 402 (77%) of the 522 trials were of low risk of outcome reporting bias, 100 (19%) of unclear risk and 20 (4%) of high risk of bias. Their assessments were based on the reporting of the review's two primary outcomes of response rates and overall dropout rates and a trial was only rated at high risk of bias in case both outcomes were missing. This is not in accordance with the Cochrane Handbook, in which a study-level judgement across all relevant outcomes is recommended.[17] According to our analyses, the review's three secondary outcomes of dropouts due to adverse events, depression symptoms measured on depression symptom scales, and remission rates were not reported in 93 (18 %) trials, 98 (19%) trials and 71 (14 %) trials, respectively. We found that a total of 182 (35%) trials did not report at least one primary or secondary outcome and, following the recommendation by the Cochrane Handbook to consider all relevant outcomes, these trials should probably have been rated as high risk of bias.[17] Selective outcome reporting leads to overestimation of the benefits and underestimation of the harms of interventions.[25]

Other bias domain

The authors omitted the 'other bias' domain from the risk of bias assessment although it is an integrated part of Cochrane's risk of bias tool.[17] Relevant biases included in this domain were baseline imbalances and design-specific risks of bias for crossover and cluster randomised trials, which were eligible according to the Cipriani *et al* protocol,[22] although the trial designs were not specified in the review.[5] Some argue that 'vested interests' should also be considered, since industry sponsored drug studies lead to more favourable effects than other studies by mechanisms that are not explained by the usual bias domains.[26] We explored whether industry sponsorship was associated with larger effect estimates, by performing random-effects meta-analyses of the placebo-controlled trials according to sponsorship using the categorisation by Cipriani *et al* (online S1 Appendix). We found a lower effect size in trials categorised as 'sponsored' (SMD of 0.27 (95% CI 0.25 to 0.30, 341 comparisons, 207 trials)) than in trials categorised as 'unclear' (SMD of 0.39 (95% CI 0.25 to 0.52, 12 comparisons, 10 trials)) and 'not sponsored' (SMD of 0.41 (95% CI 0.31 to 0.52, 37 comparisons, 36 trials)) (p=0.005 for the difference between the three estimates) (table 1).

Summary risk of bias assessment

The authors deviated from Cochrane's overall risk of bias categorisation of low, unclear or high risk of bias,[17] by introducing their own category of 'moderate' risk of bias. They classified the trials as low risk of bias if none of the domains assessed were rated as high risk of bias and three or less were rated as unclear risk; moderate if one domain was rated as high risk of bias or none were rated as high risk of bias but four or more were rated as unclear risk; and all other cases were rated as high risk of bias.[5] This approach is similar to using scales that add up scores for multiple items to produce a total, which is discouraged in the Cochrane Handbook.[17] The Handbook instead recommends an overall qualitative assessment considering the relative importance of different domains.[17] The authors rated 96 (18%) of the 522 trials as low risk of bias, 380 (73%) trials as moderate and 46 (9%) trials as high risk of bias. We were not able to replicate these findings and those efforts were made difficult because it was not clear how the blinding domains were rated in terms of risk of bias. Given that that the review's five outcomes were all likely affected by all of the risk of bias domains, the qualitative method suggested by the Cochrane Handbook involves classifying trials with any 'high risk of bias' domains as overall high risk of bias.[17] Applying these criteria (Cochrane Handbook, table 8.7.a)[17] on Cipriani *et al*'s ratings, there was one trial at low risk of bias, 383 trials (73%) at unclear risk and 138 trials (26%) at high risk of bias. When we used our classifications for the blinding domains (ie, all placebo-controlled trials were rated as unclear risk of bias, and for the selective outcome reporting domain), there were no (0%) trials at low risk of bias, 261 (50%) trials of unclear risk and 261 (50%) trials of high risk of bias (online S1 Appendix). If the three blinding domains were rated as high risk of bias in the placebo-controlled trials, rather than unclear risk of bias, there were no (0%) trials at low risk, 108 trials (21%) of unclear risk and 414 trials (79%) of high risk of bias (online S1 Appendix).

Publication bias

Publication bias of antidepressant trials is pervasive and distorts the evidence base.[9] Many industry funded

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Table 1 Random-effects pairwise meta-analyses of antidepressants versus placebo.

	N trials	N comparisons	ES	95% CI	Tau^2	I^2
Overall (SMD)						
Overall	253	390	0.29*	0.27 to 0.31	0.038	40.1%
Overall (mean difference on the HAMD17)						
Overall	109	166	1.97**	1.74 to 2.21	1.896	27.6%
Publication status						
Published	196	294	0.33*	0.30 to 0.35	0.037	40.0%
Unpublished	57	96	0.15*	0.11 to 0.19	0.020	0.0%
'Placebo run-in'						
Yes	142	221	0.31*	0.28 to 0.34	0.043	35.0%
Unclear	79	120	0.29*	0.25 to 0.33	0.032	47.6%
No	30	46	0.22*	0.16 to 0.29	0.032	35.5%
Sponsorship						
Sponsored	207	341	0.27*	0.25 to 0.30	0.033	35.4%
Unclear	10	12	0.39*	0.25 to 0.52	0.026	33.0%
Not sponsored	36	37	0.41*	0.31 to 0.52	0.075	55.7%

*SMD
**Mean difference on 17-item Hamilton depression rating scale.
ES, effect size; HAMD17, 17-item Hamilton depression rating scale; I^2, inconsistency; Tau^2, estimate of overall heterogeneity; SMD, standardised mean difference.

antidepressant trials remain unpublished or are inadequately reported.[9] Cipriani *et al*[5] included 436 published and 86 unpublished studies, but as many as a thousand antidepressant studies may have been conducted.[13] We did a random-effects meta-analysis of the placebo comparisons according to publication status and found that the average effect size was lower in unpublished studies (SMD 0.15 (95% CI 0.11 to 0.19, 96 comparisons, 57 trials)) than in published studies (SMD 0.33 (95% CI 0.30 to 0.35, 294 comparisons, 196 trials)) (p<0.0001 for difference between the two estimates) (table 1). Our findings are very similar to those reported by Turner *et al*[9] in 2008 of published versus unpublished antidepressant trials registered by the United States Food and Drug Administration (FDA) who found an SMD of 0.37 (95% CI 0.33 to 0.41) for published studies and 0.15 (95% CI 0.08 to 0.22) for unpublished studies. This indicates that the reported effect sizes by Cipriani *et al*[5] are likely inflated due to publication bias. They correctly downgraded their confidence in the evidence due to the risk of publication bias, but it would also have been appropriate to estimate the impact of publication bias on their effect estimate.

Trial duration and long-term effects

Cipriani *et al*[5] extracted outcome data as close to 8 weeks follow-up as possible within an interval of 4–12 weeks,[5] but they did not provide a rationale for this decision.[22] The common clinical practice is to prescribe antidepressants for much longer periods. In the Netherlands, 43% of SSRI (Selective serotonin reuptake inhibitor) users receive treatment for 15 months or more,[27] while 68% of those who use antidepressants in the USA take them for 2 years or more, and 25% take them for >10 years.[3] Although the short trial duration was acknowledged by the authors as a limitation, the lack of clinical relevance of such short follow-up should have been highlighted and the confidence in the evidence should have been downgraded one level in the GRADE domain of 'indirectness'. A more appropriate method would have been to extract outcome data according to length of treatment and follow-up to assess any change in the treatment effect over time. According to the trial characteristics reported by Cipriani *et al*,[5] 12 (4%) of the 304 placebo-controlled trials lasted >12 weeks. However, we found that only four of these 12 trials contained an uninterrupted double-blind, placebo-controlled phase of >12 weeks (online S2 Appendix). The two placebo-controlled trials with the longest follow-up included 81 participants at 36 weeks (online S2 Appendix). A further consequence of a short follow-up period is an underestimation of serious and non-serious adverse events.[28]

Placebo run-in and inclusion of already treated patients

The placebo run-in study design distorts the estimates of benefits and harms (box 1). Cipriani *et al* did not provide a clear definition of a placebo run-in,[22] but they characterised 260 (50%) of the 522 included trials as having a placebo run-in, 182 (35%) trials as unclear and 80 (15%) trials as having no placebo run-in.[5] We performed random-effects meta-analyses of the placebo-controlled trials according to the use of a placebo run-in design and found that the effect sizes differed between the groups with an SMD of 0.31 (95% CI 0.28 to 0.34, 221 comparisons, 142 trials) in trials with a placebo run-in, an SMD

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Box 1 'Placebo run-in', minimal clinically significant difference, and 'response' as an outcome.

A. Placebo run-in and the inclusion of already treated participants distort the benefit–harm balance.

Cipriani *et al*[5] did not provide a definition of placebo run-in, but it usually involves that the participants, before the randomisation, receive placebo, typically for about a week after which non-adherent participants and those who responded well to the placebo (often called 'placebo-responders') are excluded from the trial. Participants already in treatment with antidepressants, including the study drug, are virtually always allowed to enter the trial, and commonly all participants are tapered off ongoing antidepressant medication during the placebo run-in. This study design may impact the effect estimates of placebo-controlled trials and the benefit/harm balance through several mechanisms that favour the drug over placebo:

- Participants treated with the study drug, or a similar drug, prior to inclusion and subsequently randomised to the drug will most likely tolerate it and experience fewer harms compared with a drug naïve population (*reduced harms in the drug group*).
- Participants treated with an antidepressant before the trial and subsequently randomised to placebo might experience withdrawal symptoms that can be misinterpreted as signs of worsening of the depression or as adverse events.[44] Withdrawal symptoms typically occur within a few days after discontinuation but there is great clinical variation[44] (*reduced benefits and increased harms in the placebo group*).
- Participants already treated with an antidepressant and subsequently randomised to the study drug might experience withdrawal symptoms during the placebo run-in that are alleviated by the study drug.[44] It could be misinterpreted as an improvement of the depression (*increased benefits in the drug group*).

B. 'Response rates' lack clinical meaning.

The response rate is usually defined as the number of participants in a randomised clinical trial who achieve a reduction of >50% of the total score on a standardised observer-rated scale for depression, such as the Hamilton depression rating scale or the Montgomery-Åsberg rating scale. 'Non-response' does not necessarily imply that the participant's condition has not improved, but simply that the improvement is rated to be <50% reduction. The difference might be as little as one point on the rating scale between a 'responder' and a 'non-responder'. Thus, participants classified as non-responders may actually have shown substantial improvement. The difference in response rates between antidepressants and placebo does therefore not indicate the difference in the number of participants who have improved, but only the difference in the number of participants whose improvement exceeded the arbitrarily defined threshold. In addition, by focusing on the number of participants crossing the 50% reduction threshold the participants whose conditions deteriorate during the trial are ignored. Therefore, it seems more clinically meaningful to look at the average effect estimate of the drug compared with placebo.

C. Minimal clinically relevant difference.

Cipriani *et al* reported an overall effect estimate measured as a standardised mean difference (SMD) of 0.3 between antidepressants and placebo.[5] The British' National Institute of Health and Clinical Excellence suggested in 2004 a difference of three points on the Hamilton depression rating scale, or a SMD of 0.5, as a clinically significant change.[6] However, this difference was arbitrary and not based on empirical data.[45] Leucht *et al* used clinical trial data in 2013 to suggest that clinicians are unable to detect reductions on the Hamilton depression rating scale of three points or less.[46] Others have interpreted the same data and suggested that changes of seven points or more on the Hamilton scale, corresponding to a SMD of at least 0.875, are necessary for a clinician to detect a minimal clinical improvement.[47] We found that the mean difference between antidepressants and placebo on the 17-item Hamilton depression rating scale (range 0–52 points), based on Cipriani *et al*'s data,[5] was 1.97 points.

Continued

Box 1 Continued

of 0.29 (95% CI 0.25 to 0.33, 120 comparisons, 79 trials) where the use of a placebo run-in was unclear and an SMD of 0.22 (95% CI 0.16 to 0.29, 46 comparisons, 30 trials) in trials without a placebo run-in (p=0.05 for the difference between the three estimates). In a further subgroup analysis of unpublished trials without placebo run-in, the effect size was very small (SMD 0.08, 95% CI −0.27 to 0.11, eight comparisons, five trials). The use of the placebo run-in design and its implications were not discussed by Cipriani *et al*.[5]

Dropout as a proxy for harms

Overall dropout rates and dropouts due to adverse effects were assessed by Cipriani *et al* as measures of 'acceptability' and 'tolerability', respectively, whereas the antidepressants' actual harms and serious and non-serious adverse events were not assessed. It can be meaningful to use total dropout rates as a measure of the overall benefit/harm balance, but due to the biases introduced by including participants who are already known to tolerate an antidepressant drug and the use of a placebo run-in, this outcome will likely be biased in favour of the active drug (box 1). Furthermore, by not including a careful analysis of the serious harms, which include aggression, suicide and death,[29] and of specific adverse events, the review provided no basis for balancing the benefits and harms, which is essential for informed consent and shared clinical decision-making and for evaluating the drugs' clinical value. Adverse effects of antidepressants are common and a recent meta-analysis of 131 trials of SSRIs for depression found an increased risk of serious adverse events compared with placebo (OR 1.37; 95% CI 1.08 to 1.75).[7] This is likely an underestimate, as only 44 of the 131 included trials reported these data[7] and as serious harms, including death, of antidepressants are often not reported in published papers.[30]

Except for two drugs none of the included antidepressants had statistically significant lower total dropout rates than placebo.[5] However, Cipriani *et al* likely underestimated the antidepressants' total dropout rates since they were missing in 58 (11%) of the trials and the dropout rates due to adverse events were missing in 93 (18%) of the trials. A meta-analysis of dropouts in 73 trials based on clinical study reports obtained from drug regulators, rather than published data, showed that 12% more participants dropped out on antidepressants than on placebo.[31]

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We had access to the clinical study reports for 19 of the 522 trials included in Cipriani *et al*'s review. The outcomes of total dropout rates and dropout rates due to adverse events were fully reported in all 19 clinical study reports. In comparison with those data, total dropout rates or dropouts due to adverse events were either not reported or incorrectly reported by Cipriani *et al* in 12 (63%) of the 19 trials: total dropout rates were not reported for two trials and incorrectly reported for seven trials; dropouts due to adverse events were not reported for five trials and incorrectly reported for three trials (online S1 table).

Lack of patient relevant outcomes

Patient relevant outcomes such as quality of life and sick leave are rarely measured and reported in psychiatric drug trials. Instead, the trials mostly rely on investigator-rated symptom scores, although self-rated symptom scales also exist. In a systematic review of SSRIs for depression in adults, only six of 131 trials reported quality of life data[7] and even clinical study reports are unreliable because of selective reporting of this outcome.[31] The inability to cope with daily activities and the drugs' side-effects may be more important to patients than their depressed mood[32] and the exclusion of patient-relevant outcomes in the protocol[22] is a major limitation of the evidence and of Cipriani *et al*'s overall conclusion.[5]

Clinically irrelevant efficacy outcomes

The network meta-analysis' primary efficacy outcome was response rate (box 1). It is a problematic outcome because it lacks clinical relevance and it may create an illusion of clinical effectiveness.[33] Dichotomisation of outcomes measured on rating scales leads to loss of statistical power, and it increases the risk of false positive results[34] and spuriously inflated effect sizes.[33] Therefore, methodologists discourage the use of such dichotomised outcomes and they should generally be avoided when rating scale data are available.[34] These issues also apply to the review's secondary outcome of remission rates. The choice made by Cipriani *et al*[5] to report only the relative ORs and not the trials' absolute response rates has been criticised.[35] However, even the absolute response rates are of limited clinical relevance. Cipriani *et al*[5] did not address the problems related to 'response' and remission rates.

Statistical versus clinical significance

Cipriani *et al*[5] also reported the SMD on symptom rating scales, which is more meaningful than the dichotomised outcomes.[33 34] They reported an overall SMD for antidepressants versus placebo of 0.30 (95% credible interval 0.26 to 0.34), but the number of trials and comparisons were unclear.[5] We found a similar overall SMD for antidepressants versus placebo for the direct pairwise comparisons of 0.29 (95% CI 0.27 to 0.31, 390 comparisons, 253 studies) (table 1). These effect estimates are statistically significant, but likely below what could be considered a clinically relevant effect (box 1). We also calculated an overall mean difference for the trials that reported endpoint or change scores on the 17-item Hamilton depression rating scale, which was the most commonly used scale in the included trials (online S2 table). The mean difference between antidepressants and placebo was 1.97 points (95% CI 1.74 to 2.21, 166 comparisons, 109 trials) on the 17-item Hamilton depression rating scale (range 0–52) (table 1). This mean difference on the Hamilton scale is likely also below what could be considered a clinically relevant effect (box 1). Cipriani *et al* did not discuss the clinical significance of their reported effect size.[5]

Selected, non-representative study populations

Antidepressant trials typically have extensive exclusion criteria that limit their external validity. These include psychiatric comorbidities, alcohol abuse, long duration of illness and 'non-response' to previous antidepressant treatment.[36] The majority of patients in a clinical setting would not be eligible to enter randomised trials due to such exclusion criteria,[37] and the evidence coming from these trials is therefore of limited relevance. Furthermore, the exclusion of previous 'non-responders' and inclusion of those who are expected to respond more favourably to treatment may bias the trials (box 1). These issues were not considered by Cipriani *et al*[5] but should arguably have resulted in downgrading of the confidence in the evidence in the GRADE domain of indirectness.[18]

The certainty of the evidence

Cipriani *et al*[5] assessed the certainty of evidence for the two main outcomes using the GRADE approach adapted for network meta-analyses. They provided the GRADE results for the head-to-head comparisons, but we were unable to find the results for the placebo comparisons.[5]

Following the issues related to the quality of the evidence, the certainty of evidence for the placebo comparisons should arguably be downgraded two levels due to a 'high risk' of bias, two levels in the domain of indirectness due to short trial lengths, strict inclusion criteria and the use of placebo run-in, in addition to downgrading one level due to publication bias as acknowledged by Cipriani *et al*.[5] Downgrading due to the indirectness of the network meta-analysis' methodology should also be considered.[38] Taken together, the certainty of evidence should be 'very low'.[18]

DISCUSSION

We have identified several important biases that were not taken into account in the systematic review by Cipriani *et al*.[5] We showed that the reported effect of antidepressants over placebo measured on depression rating scales was small and likely inflated by several methodological limitations in the trials. For the first time, we showed that the placebo run-in study design appears to work towards producing inflated effect sizes, in addition to publication bias and other methodological limitations. Further, we showed that the outcome data reported by Cipriani *et al* differed from the clinical study reports and that their risk of bias assessment did not follow the methods outlined in the Cochrane Handbook. Finally, we found

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that the certainty of evidence for antidepressants versus placebo for all outcomes assessed should be very low. Taken together, the evidence does not support definitive conclusions regarding the efficacy of antidepressants for depression in adults, including whether they are more efficacious than placebo for depression.

Previous meta-analyses (figure 1) have found similar improvement in symptom scores as Cipriani *et al*.[5] Several of these reviews have considered carefully the methodological limitations, assessed the harms and have drawn different conclusions.[6–8] We found that Cipriani *et al* did not assess the risk of bias in accordance with the Cochrane Handbook as stated[5] and their results were non-transparently presented. While the authors should be commended for sharing their data, most of the review's results cannot be reproduced because basic information, such as the number of included studies, arms and participants for each meta-analysis, was not reported. The network meta-analysis methodology may hold some promise, but only in areas where clearly effective interventions exist and need to be ranked, and the many statistical options should never overshadow an initial critical assessment of the evidence and a clear presentation of the results. It seems misleading to rank the antidepressants when we have very low confidence in the evidence. Interestingly, our pairwise meta-analysis of improvement on symptom scores yielded very similar results to those reported by Cipriani *et al*. The added benefit of the network meta-analysis methodology therefore seems unclear.[5]

We found that the evidence base consists of mainly short-term trials (12 weeks or less) with no evidence for treatment beyond 36 weeks, although most patients are treated for years.[3 27] Further, the apparent effect of antidepressants reported in the review by Cipriani *et al*[5] measured on investigator-rated symptom scales was small and likely not clinically relevant. Observational studies also indicate that the effectiveness of antidepressants in practice is very low: in the large, publicly funded, Sequenced Treatment Alternatives to Relieve Depression study, only 3% of the 4041 enrolled patients were considered 'in remission' after 1 year.[39] The recent finding based on clinical study reports of randomised trials that more participants drop out on antidepressants than on placebo,[31] further suggests that the benefits of antidepressants may not outweigh the harms.

Our findings showed that Cipriani *et al*'s data[5] were inaccurate, and their estimates may therefore be incorrect because they relied on published data. It may be perceived as a limitation that we relied on the data by Cipriani *et al* and did not perform our own separate systematic literature search and data extraction. Considering the multiple methodological limitations we have identified, it would be necessary to analyse data based on clinical study reports and individual patient data to make a reliable assessment of the benefits and harms of antidepressants because they are the most reliable source of trial data.[40] There are also some limitations to our sponsorship subgroup analysis: while industry sponsored studies have been found to report favourable efficacy results more often than non-industry sponsored studies,[26] our analysis showed that industry sponsored trials reported a lower effect estimate of antidepressants compared with placebo than non-industry sponsored trials on investigator-rated depression symptom scales. However, there were important differences between the two subgroups that likely contributed to the observed difference (online S1 figure). Non-industry sponsored trials were smaller and older than industry sponsored trials and almost all of the non-industry sponsored trials included by Cipriani *et al* were published.

Our results highlight that the many hundreds of placebo-controlled trials of antidepressants have not addressed the most important, patient-relevant questions regarding antidepressants' benefits and harms. Although this has been known for years,[13] it has not led to changes in research practice. Erroneous conclusions that antidepressants are efficacious for depression have the effect that they may prevent people suffering from depression from seeking other solutions to alleviate their condition, such as psychotherapy and dealing with psychosocial stressors, and they may stall funding and research of such treatment modalities. Importantly, such conclusions may also lead to a loss of interest in providing a better evidence base to determine the true clinical value of antidepressants.

Our review has two implications. First, the review by Cipriani *et al*[5] and its conclusion should be carefully revisited. In the light of our findings, the review should not inform clinical practice. Second, our reanalysis has highlighted the need for a radical change in the way antidepressant trials are being conducted, reported and interpreted. We hope that doctors, patients, peers and politicians will consider the limitations of the current evidence of antidepressants for depression that we have presented and collectively act accordingly. This involves informing the patients about the limitations of the current evidence, thus providing a basis for a true informed consent, and working towards a better evidence base for the use of antidepressants in the treatment of depression. To get reliable answers about the antidepressants' benefits and harms in adults with depression, we need large-scale, industry-independent and better blinded, long-term trials of drug naïve participants, with patient-relevant outcomes rather than ranking scales.

Acknowledgements We are grateful to Luis Carlos Saiz, Pharm D, PhD for valuable comments.

Contributors KM, ASP-M and KB contributed to the conception and design of the study. KM performed the meta-analyses. KM, ASP-M and KB analysed and interpreted the data, drafted and critically revised the manuscript and approved the final version to be published. All authors had full access to all the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding The study was funded by the Nordic Cochrane Centre. The research was designed, conducted, analysed and interpreted by the authors entirely independently of the funding source.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All data files and the code for the statistical analyses are available from the Open Science Framework database (https://osf.io/3prz9/?view_only=0012d96af77e435f90e77755f728551a).

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Considering the methodological limitations in the evidence base of antidepressants for depression: A reanalysis of a network meta-analysis

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S1 Appendix

Risk of bias

Blinding of the participants

Cipriani et al.[1] classified three [2-4] out of the 522 trials as being at low risk of bias in the "blinding of participants" domain:

Brunoni et al.[2] tested the blinding, by asking the participants who completed the trial to guess their allocation. They reported that 39 (75%) of 52 participants on placebo, and 29 (58%) of 50 participants on sertraline were able to correctly guess their allocation. Brunoni et al. suggested that the results were "driven by clinical improvement… rather than blinding failure" [2]. We disagree and would categorise this trial at high risk of blinding bias of the participants.

Edwards et al.[3] did not describe how and when they tested the blinding, and two of the included participants were not asked. They reported that 12 (60%) of 20 participants on placebo and 12 (63%) of 19 participants on paroxetine were able to correctly guess their treatment allocation. Edwards et al. concluded that their results "confirmed the blindness of the study", but we would categorise the trial to be at unclear risk of bias.

Schatzberg et al.[4] did not test the blinding, and it is unclear why this trial was rated at low risk of bias, rather than the "stated but not tested" categorisation.

Other bias domain

While Cipriani et al.[1] categorised each arm individually according to sponsorship, we considered sponsorship on the study level: trials with any sponsored arm (as categorised by Cipriani et al.[1]) were categorised as "sponsored"; of the remaining trials, those with any arms categorised as "unclear" we labelled "unclear" and the remaining trials were categorised "not-sponsored".

Summary risk of bias assessments

Criteria for assessments

To categorise the 522 trials included by Cipriani et al.[1], we followed the Cochrane Handbook's criteria for an overall risk of bias assessment.[5] Each domain in the risk of bias tool likely affects all five included outcomes assessed by Cipriani et al., and we therefore considered all bias domains as "key domains", according to table 1.

Table 1. Criteria for overall risk of bias assessment.

Low risk of bias	All key domains classified as low risk of bias
Unclear risk of bias	One or more key domains classified as unclear risk of bias, and no domains classified as high risk of bias.
High risk of bias	One or more key domains classified as high risk of bias

We collapsed the three blinding domains in our Excel dataset and used the following criteria for our categorisation: All placebo-controlled trials were classified as unclear risk of bias in the main analysis and as high risk of bias in the sensitivity analysis. Trials that only contained head-to-head antidepressant arms, and no placebo arm, were rated as low risk of bias if the three blinding domains were rated as 'low' or 'stated but not tested' by Cipriani et al.[1]. We rated the collapsed blinding domain as unclear risk of bias, if one or more of the blinding domains were rated as unclear by Cipriani et al. Trials with missing data for any of the five included outcomes were categorised as high risk of bias. For the remaining bias domains, we adopted the categorisations by Cipriani et al.[1]. Our results are compared with Cipriani et al.'s in table 2.

Table 2. Comparison of the overall risk of bias assessments.

Cipriani et al. overall assessment		**Our overall assessments**			
		Cochrane categorisation	Sensitivity analysis using the Cipriani et al. categorisation	Our assessment	Sensitivity analysis of the blinding domains
Low risk	46 trials (9%)	Low	1 trial (0.2%)	0 trials (0%)	0 trials (0%)
"Moderate" risk	380 trials (73%)	Unclear	383 trials (73%)	261 trials (50%)	108 (21%)
High risk	96 trials (18%)	High	138 trials (26%)	261 trials (50%)	414 (79%)

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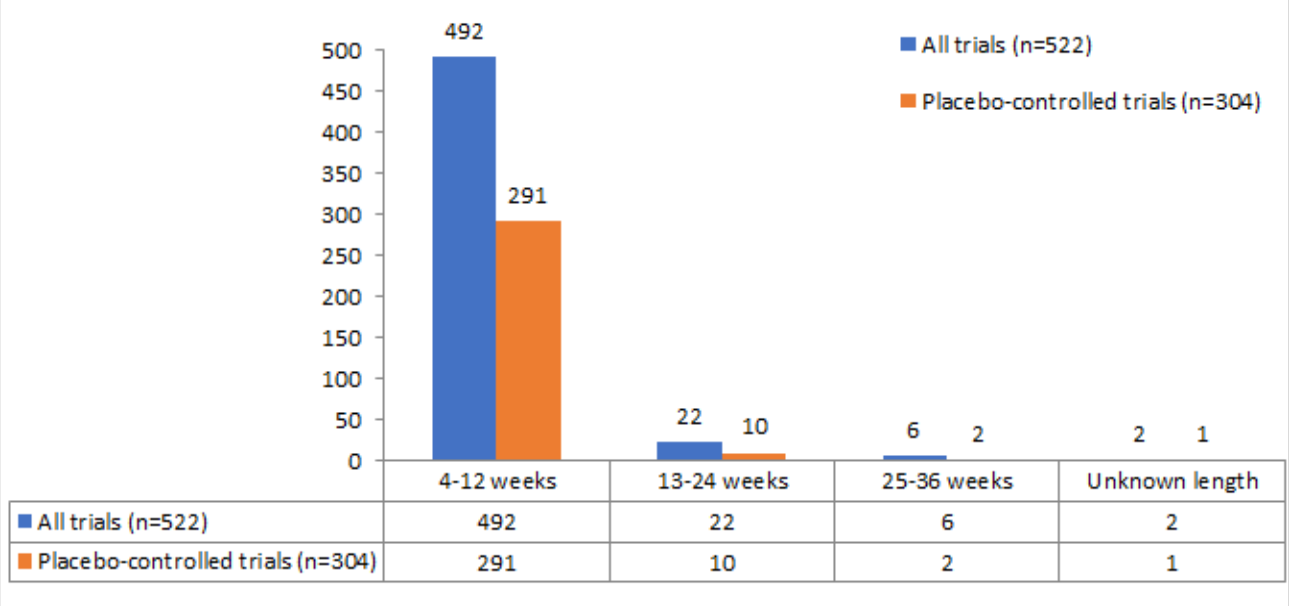
S2 Appendix

Trial duration and long-term effect estimates

Overall trial length

According to the trial characteristics by Cipriani et al.[1] 492 (94%) of the 522 included trials lasted between four and 12 weeks (figure 1), 28 trials (5%) lasted more than 12 weeks, and the trial duration was unclear for two trials (table 3).



	4-12 weeks	13-24 weeks	25-36 weeks	Unknown length
All trials (n=522)	492	22	6	2
Placebo-controlled trials (n=304)	291	10	2	1

Figure 1. All 522 trials arranged into three follow-up periods according to Cipriani et al.'s trial characteristics: Four to 12 weeks (the period used by Cipriani et al.), 13 to 24 weeks, and 25 to 36 weeks [1].

Longer-term placebo-controlled trials

Of the 28 trials lasting more than 12 weeks, 12 trials had a placebo-controlled arm (table 3) and 16 were head-to-head trials. However, upon closer examination, eight of the 12 placebo-controlled trials consisted of several 'phases' and only four trials contained a continuous randomised placebo-controlled phase of more than 12 weeks (table 4). It is unclear why Cipriani et al.[1] did not list the correct trial length characteristics, since the various extension phases were described in the available documents, also for the unpublished trials.

Table 1. All 522 trials arranged according to the trial length characteristics by Cipriani et al.[1]

Trial length according to Cipriani et al.[1] (N = 522)	Trials without a placebo arm (N)	Placebo-controlled trials (N)
4 weeks	9	39
5 weeks	11	4
6 weeks	92	100
7 weeks	9	0
8 weeks	59	118
9 weeks	3	2
10 weeks	4	10
12 weeks	14	18
13 weeks	1	1
16 weeks	2	2
20 weeks	0	1
24 weeks	9	6

25 weeks	2	0
26 weeks	1	0
36 weeks	0	2
Trial length unknown	2	1
Total	218	304

Table 2. Longer-term placebo-controlled trials (trial length of more than 12 weeks).

Trial	Drug arm 1	Drug arm 2	Trial length according to Cipriani et al. (weeks)	Actual trial length (weeks)	Study design and phases
Oakes 2012a [2]	duloxetine	-	36	36	-
Oakes 2012b [2]	duloxetine	-	36	36	-
CL3-20098-022 [3]	agomelatine	fluoxetine	24	6 + 18	"Optional double-blind placebo-controlled extension" (page 24) for "responders to treatment" (page 26)
CL3-20098-023 [3]	agomelatine	paroxetine	24	6 + 18	"Optional double-blind placebo-controlled extension" (page 24) for "W6 responders" (page 26)
CL3-20098-024 [3]	agomelatine	fluoxetine	24	6 + 18	"Optional double-blind placebo-controlled extension" (page 24) for "responders to treatment at W6" (page 26)
CL3-20098-026 [3]	agomelatine	-	24	6 + 18	"18-week extension period" of "responders at W6" (page 42)
CL3-20098-070 [4]	agomelatine	-	24	8 + 16	16-week extension period for responders
Robinson 2014 [5]	duloxetine	-	24	12 + 12	From week 12 to 20 placebo rescue or dose increase were available
Lopez-Rodriguez 2004 [6]	fluoxetine	-	20	20	-
Barber 2011 [7]	sertraline	-	16	8 + 8	Non-responders on sertraline were switched to venlafaxin ER at week 8
Dimidjian 2006 [8]	paroxetine	-	16	8 + 8	The blind was broken at week 8 and the placebo arm was offered other treatments
Lecrubier 1997 [9]	venlafaxine	-	13	13	-

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Considering the methodological limitations in the evidence base of antidepressants for depression: A reanalysis of a network meta-analysis

Klaus Munkholm [a], Asger Sand Paludan-Müller [a], Kim Boesen [a]

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S1 Table

S1 Table. Comparison between the outcomes of total dropout rates and dropouts due to adverse events as reported by Cipriani et al.[1] and the data reported in the clinical study reports.

Trial ID (From Cipriani et al. dataset)	**Total dropouts reported by Cipriani et al. compared with clinical study reports***	**Dropouts due to adverse events reported by Cipriani et al. compared with clinical study reports****
Goldstein2002 (HMAQ - Study Group A)	Match	Match
Study F1J-MC-HMAQ - Study Group B (starting page in the pdf document: 147)	Match	Not reported
Goldstein2004a (HMAT - Study Group A, ID#4091)	Discrepancy	Match
Goldstein2004b (HMAT - Study Group B, ID#4091)	Match	Discrepancy
Detke2004 (HMAY Study Group A)	Match	Match
Perahia2006 (HMAY - Study Group B)	Match	Match
Detke2002a (HMBH - Study Group A)	Match	Match
Detke2002b (HMBH - Study Group B)	Match	Discrepancy
0600B-367	Not reported	Not reported
0600B1-384	Discrepancy	Discrepancy
VEN 600A-303 (FDA)	Discrepancy	Match
Cunningham1994 (VEN 600A-302 FDA)	Discrepancy	Match
VEN 600A-313 (FDA)	Discrepancy	Match
0600A1-372	Not reported	Not reported
Thase1997 (VEN XR 209 FDA)	Match	Match
Rudolph1998 (VEN 600A-203 (FDA)	Match	Match
SER 101 (FDA)	Match	Not reported
Fabre1995 (SER 103 FDA)	Match	Match
SER 310 (FDA)	Discrepancy	Not reported

*Our comparison considered all treatment arms in the trials. If data for all arms matched, we assigned an assessment of 'match'; if data for any arm differed but were reported, we assigned an assessment of 'discrepancy'; if data for any arm was not reported, we assigned an assessment of 'not reported'.

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S2 Table

S2 Table. Rating scales used in the included placebo-controlled trials (n = 304).[1]

Scale	Number of trials	Number of treatment arms
HAMD17	137	198
HAMD21	92	139
HAMD24	13	22
HAMD29	1	2
HAMD31	1	2
HAMD unspecified	22	25
IDS-IVR-30	1	1
MADRS	29	50
NA	8	12

NA: not available; HAMD17: 17-item Hamilton depression rating scale; IDS-IVR-30: 30-item Inventory of Depressive Symptomatology-Self Report; MADRS: Montgomery-Åsberg Depression Rating Scale.

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1. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet* 2018 doi: 10.1016/S0140-6736(17)32802-7 [published Online First: 2018/02/27]

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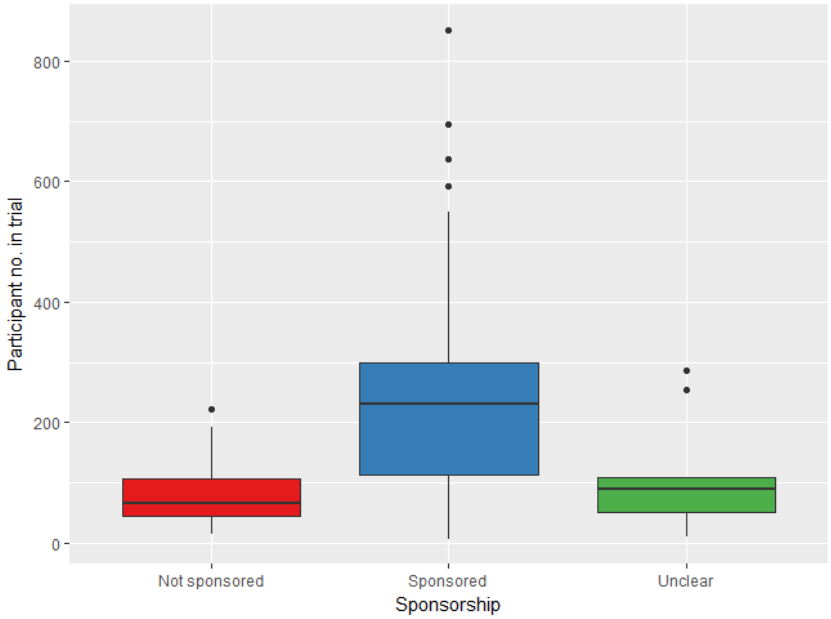
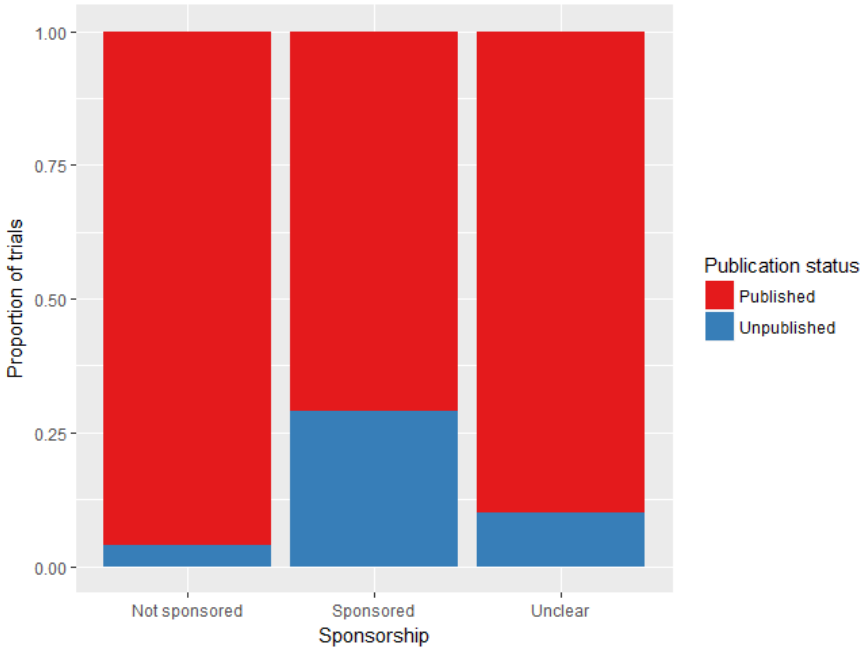
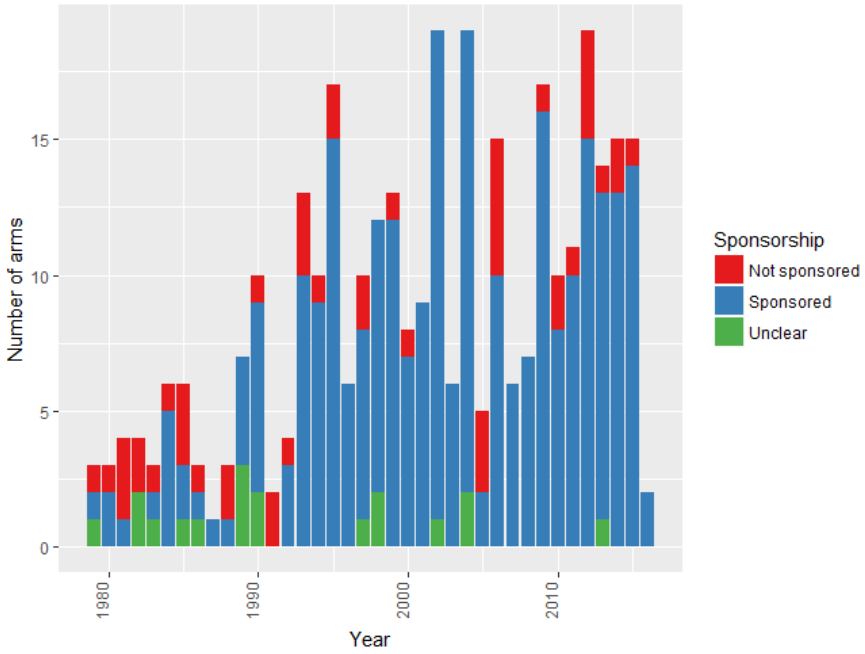
S1 Figure



S1 Figure. A Size of placebo-controlled trials in the review by Cipriani et al.[1] according to sponsorship.



S1 Figure. B Sponsorship status of placebo-controlled trials in the review by Cipriani et al.[1]



S1 Figure. C Sponsorship of placebo-controlled trials in the review by Cipriani et al.[1] according to publication year.

References

1. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet* 2018 doi: 10.1016/S0140-6736(17)32802-7 [published Online First: 2018/02/27]

Paper 3

EMA and FDA psychiatric drug trial guidelines: Assessment of guideline development and trial design recommendations

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Submitted for publication

GRADUATE SCHOOL OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

PHD-THESIS
DECLARATION OF CO-AUTHORSHIP

The declaration is for PhD students and must be completed for each conjointly authored article. Please note that if a manuscript or published paper has ten or less co-authors, all co-authors must sign the declaration of co-authorship. If it has more than ten co-authors, declarations of co-authorship from the corresponding author(s), the senior author and the principal supervisor (if relevant) are a minimum requirement.

1. Declaration by	
Name of PhD student	Kim Boesen
E-mail	kb@cochrane.dk
Name of principal supervisor	Jacob Rosenberg
Title of the PhD thesis	Methodological limitations in psychiatric drug trials with a particular focus on extended-release methylphenidate

2. The declaration applies to the following article	
Title of article	EMA and FDA psychiatric drug trial guidelines: Assessment of guideline development and trial design recommendations
Article status	
Published ☐ Date:	Accepted for publication ☐ Date:
Manuscript submitted ☑ Date: 8 July 2020	Manuscript not submitted ☐
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	

3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD-student's contribution to the article **A**. Has essentially done all the work (> 90 %) **B**. Has done most of the work (60-90 %) **C**. Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
1. Formulation/identification of the scientific problem	A
2. Development of the key methods	A
3. Planning of the experiments and methodology design and development	A
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	A
5. Conducting the analysis of data	A
6. Interpretation of the results	A
7. Writing of the first draft of the manuscript	A
8. Finalisation of the manuscript and submission	A
Provide a short description of the PhD student´s specific contribution to the article.[i] Coining idea, writing protocol, collecting data, corresponding with drug regulatory agencies, analysing data, writing frist draft, revising and finalising manuscript.	

4. Material from another thesis / dissertation[ii]	
Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?	Yes: ☐ No: ☒
If yes, please state name of the author and title of thesis / dissertation.	
If the article is part of another author's academic degree, please describe the PhD student´s and the author´s contributions to the article so that the individual contributions are clearly distinguishable from one another.	

5. Signatures of the co-authors[iii]

	Date	Name	Title	Signature
1.	8/7/2020	Peter C Gøtzsche	DSci	
2.	8/7/2020	John PA Ioannidis	DSci	
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				

6. Signature of the principal supervisor

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 13 July 2020
Principal supervisor: Jacob Rosenberg

7. Signature of the PhD student

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 13 July 2020
PhD student: Kim Boesen

Please learn more about responsible conduct of research on the Faculty of Health and Medical Sciences' website.

[i] This can be supplemented with an additional letter if needed.

[ii] Please see Ministerial Order on the PhD Programme at the Universities and Certain Higher Artistic Educational Institutions (PhD Order) § 12 (4):

"Any articles included in the thesis may be written in cooperation with others, provided that each of the co-authors submits a written declaration stating the PhD student's or the author's contribution to the work."

[iii] If more signatures are needed please add an extra sheet.

EMA and FDA psychiatric drug trial guidelines: Assessment of guideline development and trial design recommendations

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Word count: 3581

Abstract

Objectives

To assess the development and content of EMA and FDA research guidelines for the design of pivotal psychiatric drug trials.

Design

Cross sectional study.

Data source

EMA Clinical Efficacy and Safety guidelines and FDA Guidance Documents.

Main outcomes and measures

Guideline committee members' conflicts of interests; stakeholders and comments on draft versions categorised according to conflicts of interests ('industry', 'not-industry but with industry related conflicts', 'independent', 'unclear'); development of guidelines and organisation of commenting phase; recommendations regarding four trial design characteristics (trial duration, psychiatric comorbidity, "enriched design", efficacy outcomes).

Results

We included 13 EMA and five FDA guidelines covering 15 psychiatric indications. Five months after submission, the EMA had not processed our request regarding committee member disclosures. FDA offices draft the Guidance Documents, but the Agency is not in possession of employee conflicts of interest declarations because FDA employees generally may not hold financial interests (although some employees may hold interests up to $15,000). The EMA and FDA guideline development phases are similar, drafts and final versions are publicly announced and everybody can submit comments. 70 stakeholders commented on ten guidelines: 38 (54 %) 'industry', 18 (26 %) 'not-industry but with industry-related conflicts', 6 (9 %) 'independent' and 8 (11 %) 'unclear'. They submitted 983 comments: 621 (68 %) 'industry', 241 (26 %) 'not-industry but with industry related

conflicts', 36 (4 %) 'independent' and 19 (2 %) 'unclear' (66 could not be assigned to a specific stakeholder). The recommended designs were generally for trials of short duration; with restricted trial populations; allowing previous exposure to the drug; and often recommending rating scale efficacy outcomes. However, there were also important differences and FDA's recommendations regarding exclusion of psychiatric comorbidity seemed less restrictive.

Conclusions

The EMA and FDA clinical research guidelines for psychiatric pivotal trials recommend designs that tend to have limited generalisability. Independent and non-conflicted stakeholders are underrepresented in the guideline development. It seems warranted with more active involvement of scientists and independent organisations without conflicts of interest in the guideline development process.

Protocol registration

https://doi.org/10.1101/2020.01.22.20018499.

Words: 336

Summary box

What is already known on this topic

- EMA and FDA produce guidelines for the design of pivotal psychiatric drug trials
- It is unknown who are involved in the guideline development and what specific trial design recommendations they give

What this study adds

- The guideline development phases are open to the public. There was a dearth of independent stakeholders commenting on the guidelines whereas the industry seemed overrepresented
- EMA and FDA recommend trial designs with limited generalisability that may not offer optimal benefit for the public and patients

Background

Recent reports have found that newly authorised medicines often have questionable or no added patient-relevant benefits compared to older treatments.[1-6] In a cohort of drugs approved by the German drug regulatory agency between 2011 and 2016, the Institute for Quality and Efficiency in Health Care (IQWiG) judged that 10 % had substantial benefits compared to already available treatments, while 58 % had no proof of added benefits.[1] Cohort studies of oncology drugs approved by the European Medicines Agency (EMA)[4] and the US Food and Drug Administration (FDA)[5] found that most drugs were approved without clear evidence of benefits on overall mortality or quality of life. Similarly, an analysis of oncology drugs approved by the EMA between 2014 and 2016 reported that many pivotal trials underpinning drug approvals were of high risk of bias due to problems with the trial design or trial conduct.[6] It has been argued that the threshold for new drug approvals has been lowered to accommodate the pharmaceutical industry's interests,[7] and researchers have advocated for more pragmatic, patient-relevant trials.[8]

Systematic reviews, particularly of antidepressants for depression[9, 10] and of central stimulants for attention deficit hyperactivity disorder,[11-13] have highlighted potential problems with low generalisability of psychiatric drug trials, similar to those identified in pivotal oncology drug trials. Common methodological limitations in these trials are small sample sizes, short trial durations, restricted trial populations in terms of allowed psychiatric comorbidity, risk of withdrawal effects due to previous exposure to the drug of interest, and the use of surrogates and rating scales rather than patient-relevant outcomes.[9-13] In the German cohort of authorised drugs,[1] only one out of 18 newly approved drugs in the combined field of psychiatry/neurology was judged to have substantial added benefits compared to already available treatments.

The EMA and FDA publish guidelines on how to design and conduct pivotal trials for new drug approvals. EMA publishes Clinical Efficacy and Safety Guidelines, which the agency "*strongly encourages*" their applicants to follow. The guidelines "*reflect a harmonised approach of the EU Member States and the Agency on how to interpret and apply the*

requirements for the demonstration of quality, safety and efficacy […]".[14] The FDA publishes Guidance Documents, which are described as, *"Guidances are intended to assist the pharmaceutical industry in carrying out its obligations under laws and regulations on subjects such as the processing, content, evaluation, and approval of drug product applications and the design, production, manufacturing, and testing of regulated products"*.[15] The Guidance Documents are *"not legally binding or enforceable. However, guidance documents contain important Agency recommendations. Because guidance documents represent current Agency thinking, sponsor submissions that conform to current guidance should be considered acceptable"*.[15]

We wanted to systematically assess (1) the committee members behind the research guidelines and their declared conflicts of interest; (2) the stakeholders who comment on guideline draft and concept papers; (3) the organisation of the commenting phases on draft and concept papers, and (4) the FDA and EMA design recommendations for four trial characteristics in pivotal psychiatric drug trials.

Methods

Inclusion of drug regulatory agency guidelines

We applied the following inclusion criteria: the guideline (draft or final version) should be published by the EMA or FDA on how to design pivotal trials for drug approval; the guideline should cover all aspects of pivotal trial design (what the FDA calls 'umbrella guidance') and not address specific trial aspects only, e.g. inclusion criteria or specific outcome measures; the guideline should cover psychiatric diagnoses as defined in current or previous versions of the *Diagnostics and Statistics Manual of Mental Disorders* (DSM) or the *International Classification of Diseases* (ICD). We included the newest guideline (draft or final version), if more than one guideline was published on the same subject. See eMethods for details.

Guideline committee members' conflicts of interest

The FDA and EMA guideline committee members and their declared conflicts of interest are not publicly available. We filed Freedom of Information Act requests to access the

committee member lists and their declared conflicts of interest. We wanted to report the proportion of committee members with declared conflicts of interest for each guideline.

Stakeholder comment documents

EMA makes available dedicated documents with stakeholder comments submitted on draft guidelines. Comments and corresponding replies from EMA are collated in a single document and made available online.

FDA manages and operates public correspondence on federal regulations and other rule-making documents through the *Docket's Management*. All official US Federal documents, such as drafts or final Guidance Documents, have their own designated website, called a Docket Folder Summary, where the public can submit and also view submitted comments on the documents. See eMethods for details.

For each included stakeholder document, we counted the total number of stakeholders, total number of comments, and total number of comments by each stakeholder. We categorised the stakeholders according to their conflicts of interest as '*industry*', '*not-industry but with industry-related conflicts*', '*independent*', or '*unclear financial relationship*'. See eMethods for details.

Guideline development

We assessed the development of draft guidelines in regards to (1) public availability of draft versions for commenting; (2) recruitment of specific stakeholders to comment; (3) applied restrictions on who may comment on the documents; (4) announcement of publication of drafts and final guidelines, e.g. on social media, in newsletters, or in relevant journals.

We searched the FDA and EMA websites for information. It was not necessary to contact the regulators directly for additional information.

Trial design recommendations

For all included research guidelines, we extracted recommendations regarding four trial design characteristics: duration of follow-up, also after the randomised phase ended;

exclusion criteria related to psychiatric comorbidity; previous exposure to the drug or drug class; efficacy outcomes (primary and secondary).

We wanted to put each design recommendation in a clinical context, i.e. what is the natural history of the condition, what are the most common comorbid psychiatric diagnoses and how common are they, and will previous exposure to the drug affect the trials' external validity? We extracted this clinical information from the guidelines, rather than doing free-hand searches for relevant evidence, as we had outlined in the protocol. We found this to be the least biased method to evaluate the trial recommendations from a clinical perspective. We further searched the Core Outcome Measures in Effectiveness Trials (COMET) database[16] for standardised sets of outcome measures for the individual indications, and we assessed Eiring et al.'s systematic review[17] of patient preferences for outcome measures in psychiatric drug trials.

Results

Overview of results

We searched the EMA and FDA websites in February 2020 and identified 13 eligible EMA Clinical Efficacy and Safety guidelines and five FDA Guidance Documents (table 1). The 13 EMA guidelines were published between 2005 and 2017; the panic disorder guideline could not be downloaded. All EMA guidelines were adopted versions, two (insomnia and schizophrenia) had been revised once and the depression guideline had been revised twice. Concept papers for upcoming revisions were published for the depression and bipolar disorder guidelines. The five FDA guidelines were published between 2015 and 2019; four were draft versions and one (opioid use disorder) was a final guideline. The 18 guidelines covered 15 unique indications (depression, ADHD and alcohol dependence were covered by both agencies). The full dataset is available from the Excel file.

Guideline committee members' conflicts of interests

The FDA Freedom of Information Team informed us during a telephone meeting that, (1) federal employees are not allowed to have financial conflicts of interests; (2) Guidance Documents are authored internally in the Agency by divisions or offices and not by

individual employees; and (3) therefore the FDA is not in possession of conflicts of interest declarations related to Guidance Document development (see summary of correspondence in eResults). We partly confirmed statement (1) from FDA's website,[18] where it is stated that FDA employees are prohibited from holding financial interests, e.g. stocks, in any FDA "significantly regulated organization". However, there are exceptions to the rules. For instance, only designated FDA employees, called "confidential filers", are required to disclose conflicts of interest. Employees that are not required to disclose their financial conflicts of interest may hold financial interests up to 15,000 US Dollars.[18] We could not find any information relevant to statements (2) and (3) in the FDA Manuals of Policies and Procedures (MAPPs) "Developing and Issuing Guidance"[15] and "Developing indication-specific Guidances".[19] The EMA informed us they were not able to respond within their regular response time caused by EMA's relocation to Amsterdam. After five months from submission, EMA had not processed our request of access to committee member lists. See the correspondence with EMA and FDA in Supplement 2.

Stakeholder comments

There were stakeholder comments available for six of the 13 EMA research guidelines and four of the five FDA guidelines. 70 stakeholders submitted a total of 983 comments, of which 917 comments could be assigned to a stakeholder. For 66 the stakeholder was unknown, as EMA's Post Traumatic Stress Disorder (PTSD) guideline did not assign the individual comments to the stakeholder. There were 52 unique stakeholders of which two, International Society for CNS Clinical Trials and Methodology and Lundbeck, commented on both EMA and FDA documents. See full dataset for details.

EMA guidelines

38 stakeholders made 750 comments on six EMA guidelines. Six stakeholders commented on more than one guideline providing 25 unique stakeholders: Lundbeck and the European Federation of Pharmaceutical Industries and Associations commented on five guidelines each, Merck Sharp & Dome commented on three, and European College of Neuropsychopharmacology, International Federation of Association of Pharmaceutical Physicians, and Hoffman-La Roche commented on two each. We categorised 25 (66 %) stakeholders as 'industry', nine (24 %) as 'not-industry but with industry-related conflicts',

and 4 (10 %) as 'independent' (table 2). On the comment level, we categorised 517 (76 %) comments as 'industry', 148 (22 %) as 'not industry but with industry-related conflicts', 19 (3 %) as 'independent', and 66 were not categorised (table 3).

FDA Guidance Documents

32 stakeholders made 233 comments on four FDA Guidance documents. There were 29 unique stakeholders since three stakeholders, Lundbeck, Anthem Inc., and International Society for CNS Clinical Trials and Methodology commented on two guidance documents each. We categorised 13 (41 %) stakeholders as 'industry', 9 (28 %) as 'not-industry but with industry-related conflicts', 2 (6 %) as 'independent', and 8 (25 %) as 'unclear' (table 2). On the comment level, we categorised 104 comments (45 %) as 'industry', 93 (40 %) as 'not-industry but with industry-related conflicts', 17 (7 %) as independent, and 18 (8 %) as 'unclear' (table 3).

Guideline development

EMA and FDA produce their research guidelines in a similar fashion, summarised in table 4.

EMA guidelines

EMA's development of the efficacy and safety guidelines is described in the *Procedure for European Union guidelines and related documents within the pharmaceutical legislative framework*.[20] There are three stages where stakeholders may comment on the guidelines during the development: (1) first, a concept paper, which outlines the overall purpose of the guideline, is made available for commenting for three to six months. It is unclear if the concept paper is written with input from outside stakeholders; (2) then a draft guideline is made available for comments, also for three to six months; finally (3) the adopted guideline is published and may be commented on at any given time. EMA announces all documents for public consultation on a designated website called "Open consultations".[21]

FDA Guidance Documents

The Guidance development is described in the FDA Manual of Policies and Procedures "Developing and Issuing Guidance"[15] and "Developing indication-specific Guidances",[19] the Code of Federal Regulation, Part 10, Section 10.115,[22] and FDA's report on Guidance

Documents.[23] There are two stages, possibly three if the draft development is included, where stakeholders may comment on Guidance Documents: (1) First, FDA develops a draft Guidance. This can be done in collaboration with individuals or organisations outside FDA, e.g. through input from workshops or Advisory Committees. Stakeholders may also submit draft proposals directly to FDA; (2) a draft guideline is made publicly available for comments for 60 days through announcement in the *Federal Register*,[24] the official journal of the United States Government and a designated website,[25] (3) the final Guidance Document is published and announced in the Federal Register and online and may be commented on at any given time. Every year, FDA also publishes a "Guidance Agenda" containing a list of guidances they plan to publish or revise during the year.[26]

Trial design recommendations

The EMA guidelines provided recommendations for all four trial characteristics, i.e. trial duration, psychiatric comorbidity, "enriched design", and efficacy outcomes in all guidelines, except "enriched design" (alcohol dependence) and psychiatric comorbidity (bipolar disorder). None of the five FDA Guidance Documents contained recommendations for all four trial characteristics; for example previous exposure to relevant medications were described in only guideline (opioid use disorder) only. The trial recommendations for each guideline are summarised in eTable 1 to eTable 15.

Overlapping guidelines

EMA and FDA published overlapping guidelines on ADHD (eTable 3), depression (eTable 5), and alcohol dependence (eTable 10). The FDA guidelines were draft versions and did not contain recommendations on "enriched design" or on psychiatric comorbidity in the ADHD guideline. The guidelines concurred on trial durations for depression and alcohol dependence, e.g. EMA recommended 4 to 8 weeks and FDA 6 to 8 weeks in depression trials, and both agencies recommended a 6-months randomised withdrawal design to assess long-term outcomes. The EMA guidelines seemed more restrictive regarding psychiatric comorbidity, whereas the FDA depression and alcohol dependence guidelines emphasised the inclusion of relevant comorbidity. The guidelines agreed on the use of rating scales in ADHD and depression trials as efficacy outcomes and on the use of full abstinence or no heavy drinking for alcohol dependence.

Trial duration

EMA recommended short- and long-term trial durations in all 12 available guidelines. Short-term durations ranged from 2 to 14 weeks, with the exception of alcohol dependence (3-6 months) and Premenstrual Dysphoric Syndrome (6 months). Long-term durations ranged from 3 to 15 months, of which 7 guidelines recommended the randomised withdrawal design, three guidelines (ADHD, insomnia, alcohol dependence) recommended a placebo-controlled trial or the randomised withdrawal design, and two guidelines did not recommend any particular design (bipolar disorder and premenstrual dysphoric disorder).

The FDA recommendations were more varied; 6 to 8 weeks for depression, 24 weeks for "low sexual interest and/or arousal in women", 6 months for alcohol dependence, and for ADHD they only gave a recommendation for long-term safety trials of 12 months to assess the effect on growth in children.

Psychiatric comorbidity

EMA listed extensive exclusion criteria related to psychiatric comorbidity in 10 of the 12 available guidelines. Two guidelines (bipolar disorder and depression) did not specify exclusion criteria.

The three FDA Guidance Documents (depression, alcohol dependence, "low sexual interest and/or arousal in women") containing recommendations on psychiatric comorbidity were less restrictive and stated that unnecessary restrictions should be avoided.

"Enriched design"

All EMA guidelines, except alcohol dependence, specified that participants could have been exposed to relevant medication prior to enrolment and there should be a "washout" of such drugs.

Only one FDA Guidance Document (opioid use disorder) referred to previous exposure by stating, "patients should be either new entrants to treatment or stable on other treatments".

Efficacy outcomes

Ten EMA guidelines recommended symptom-rating scales as efficacy measures. The alcohol dependence guideline recommended full abstinence or no heavy drinking, and the insomnia guideline recommended self-rated sleep, polysomnography and quality of life. Several guidelines stipulated the use of responder analyses.
The FDA Guidance Documents recommended rating scales for two indications (depression and ADHD), no heavy drinking or full abstinence (alcohol dependence), urine toxicology (opioid use disorder), and number of satisfying sexual events or self rating of sexual interests, arousal and distress (low sexual interest and/or arousal in women).

Discussion

Principal findings

This is the first study to systematically assess the development and content of regulatory research guidelines for psychiatry. These guidelines are intended for industry, but the dearth of non-industry stakeholders was surprising considering the guideline process being apparently open to public comments. The FDA launched in 2010 a "Transparency Initiative"[23] and one of the objects were to improve stakeholder involvement. FDA's stakeholder composition was more varied than EMA's, although still dominated by stakeholders with conflicts of interest.

The guidelines encouraged the design of clinical trials with limited generalisability, which may contribute to research waste.[27] Most recommended trial durations were short and both agencies recommended the randomised withdrawal design for long-term trials. In such a trial, participants who benefit from a drug either in a placebo-controlled trial or in an open-label phase are randomised to continued active drug or placebo.[28] Abrupt stopping of psychotropic drugs can lead to withdrawal symptoms, e.g. after use of antidepressants[29] or central stimulants, which carries an FDA black box label warning about the risk of drug dependence.[30] If these drugs are not tapered off slowly, the withdrawal symptoms may be misinterpreted as symptom deterioration and superiority of the drug over placebo. In FDA's opioid use disorder guideline it was stated, "*Sponsors can conduct trials in patients already stable on other treatments*". This indicates that participants who are adequately treated before the trial may be randomised to placebo and thereby risk experiencing withdrawal

symptoms. In EMA's schizophrenia guideline it was stated, "typically a few days will be appropriate" for washing out prior antipsychotic medication during a placebo lead-in, which seems to be insufficient to avoid withdrawal symptoms.

Most EMA guidelines recommended extensive exclusion criteria regarding psychiatric comorbidity. The obsessive-compulsive disorder (OCD) guideline described that the population should be "pure" OCD but the guideline also highlighted, "*lifetime co-morbidity rates of other psychiatric diseases in patients with OCD range from 75 to 84%"*. The ADHD guideline stated, "another Axis I disorder", "severe comorbid symptoms such as depression and anxiety" or "primary axis II disorder" as exclusion criteria. Such elaborate exclusion criteria reduce the trials' generalisability,, e.g. most patients diagnosed with ADHD[31] or depression[32] are not eligible for inclusion in pivotal clinical trials. The FDA Guidance inclusion criteria were less restrictive and emphasised the inclusion of participants with comorbidities. In 2019, FDA published a draft guideline entitled "Enhancing the diversity of clinical trial populations"[33] and the Agency seems cognisant of the problem of restricted trial populations, "*Sponsors should adopt practices for determining eligibility criteria that will allow the clinical trial population to reflect the diversity of the patients who will be using the drug if the drug is approved*".[33]

We found that EMA and FDA mostly recommended surrogate outcomes. A recent analysis[34] similarly reported that 21 of 27 FDA anti-infective Guidance Documents recommended surrogate outcomes rather than patient-relevant outcomes such as mortality.

Implication for practice and research

We identified several cases where the agencies seemed to prioritise the interests of the applicants rather than the public. For instance, FDA wrote in their opioid use disorder guideline, "*There is great public heath interest in assessing additional, clinically meaningful endpoints such as reduction in hospitalizations, emergency department visits, overdose, and death, as well as improvements in the ability to resume work, school, or other productive activity. Though understanding these outcomes would be highly valuable, the Agency recognizes that evaluating these outcomes could require larger trials than those usually conducted for marketing approval".* If the agencies wish to serve the public, the required

pivotal trials should reflect the interests of the public and thus address real-world patient populations and patient-centered outcomes.

FDA informed us that their employees cannot have conflicts of interests. The FDA policy allows non-designated employees to have assets up to 15,000 US Dollars.[18] Five months after we submitted our request regarding access to the committee members' conflicts of interest, EMA had not processed it. It would be useful for regulatory agencies to make such information publicly available to increase transparency.

Study limitations

The sample of guidelines was small and there was an uneven distribution of stakeholders and comments. There were challenges in counting the number of FDA comments due to the non-uniform format, and we were unable to access a few guidelines and stakeholder documents. We recognise the large variations in the stakeholder comments and that different criteria for quantifying the comments would yield different counts. However, count differences would have been relatively minor and unlikely to change the overall results. We were also unable to identify several of the individual commenters who submitted comments on the FDA Guidance Documents, since their affiliations were not disclosed. We did not compare draft and final guidelines to assess if, and how, the submitted stakeholder comments might have served specific industry interests. We believed that such analyses would be too subjective.

It was a challenge to separate the stakeholders according to their conflicts of interest, especially patient groups and organisations. Some evidence points to a dose-response relationship between conflicts of interests and drug prescription patterns,[35] and a recent systematic review reported that industry funding of patient organisations is common.[36] We did therefore not define a lower monetary threshold, but categorised stakeholders as 'not-industry but with industry-related conflicts 'if we identified any conflict of interest.

Conclusion

The EMA and FDA clinical research guidelines for psychiatric pivotal trials recommend designs that tend to have limited generalisability. Independent and non-conflicted stakeholders are underrepresented in the development phases and current guidelines emphasise trials with limited scope that may not offer much clinical value. EMA and FDA should reconsider their guideline development and find ways to promote greater involvement of the public and independent stakeholders. This may require greater advertisement of the guideline process to the public and active invitation of large numbers of scientists and organisations that are known to have no conflicts of interest to comment on the guidelines.

Declarations

Conflicts of interest

None.

Acknowledgements

We thank the METRICS lab meeting participants for insightful comments on the draft protocol.

Contributions

KB conceived the idea, collected and analysed data, corresponded with the drug regulatory agencies, and wrote the first draft. JPAI and PCG contributed to the design of the study, commented and supervised the final manuscript. All authors critically revised the final manuscript. All authors approved the final version. KB is the guarantor.

Funding

METRICS is supported by a grant from the Laura and John Arnold Foundation and METRIC B is supported by a visiting Einstein fellowship in the Berlin Institute of Health to John Ioannidis from the Einstein Foundation and the Stiftung Charité (JPAI).

Ethics approval

Not applicable

Transparency Statement

The project protocol was made available 27 January 2020 on medRxiv (https://www.medrxiv.org/content/10.1101/2020.01.22.20018499v1). The full dataset is available as an Excel file from the Open Science Framework (*insert link upon publication*). Any questions regarding the dataset should be sent to the corresponding author.

KB affirms that the manuscript is an honest, accurate, and transparent account; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

Patient and public involvement

We did not involve patients or the public in this research project

Dissemination to participants and related patient and public communities

We plan to present our findings to relevant pubic and private organisations to discuss how to improve involvement of patients and the public in the development of regulatory guidelines

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Table 1. Overview of included regulatory research guidelines

Regulator	Condition	Guideline ID	Year of publication	Draft or final guideline
EMA	Autism Spectrum Disorder	EMA/CHMP/598082/2013	2017	Final
EMA	Depression	CHMP/185423/2010 Rev. 2	2013	Final (revision 2)[a]
EMA	Schizophrenia	CHMP/40072/2010 Rev. 1	2012	Final (revision 1)
EMA	Insomnia	CHMP/16274/2009 Rev. 1	2011	Final (revision 1)
EMA	Premenstrual Dysphoric Disorder	CHMP/607022/2009	2011	Final
EMA	Attention Deficit Hyperactivity Disorder	CHMP/EWP/431734/2008	2010	Final
EMA	Alcohol Dependence	CHMP/EWP/20097/2008	2010	Final
EMA	Post Traumatic Stress Disorder	CHMP/EWP/358650/2006 Corr. 2	2008	Final
EMA	Social Anxiety	CHMP/EWP/3635/2003	2006	Final
EMA	Obsessive Compulsive Disorder	CHMP/EWP/4279/2002	2005	Final
EMA	Generalised Anxiety Disorder	CPMP/EWP/4284/2002	2005	Final
EMA	Panic Disorder	CHMP/EWP/4280/2002	2005	Final[b]
EMA	Bipolar Disorder	CPMP/EWP/567/1998	2001	Final[a]
FDA	Attention Deficit Hyperactivity Disorder	2019-09193	2019	Draft
FDA	Opioid Use Disorder	FDA-2018-D-1334	2019	Final
FDA	Major Depressive Disorder	FDA-2018-D-1919	2018	Draft
FDA	Low sexual interest, and/or arousal in women	No ID	2016	Draft
FDA	Alcoholism	FDA-2015-D-0152	2015	Draft

Listed in order of publication year. [a)] a concept paper for a revision of the guideline has been published. [b)] The link to the guideline did not work so we could not include and assess the actual guideline.

Table 2. Stakeholder categorised by conflicts of interest

Regulator	**Guideline**	**No. stakeholders**	**'Industry' (%)**	**'Not-industry but with industry-related conflicts' (%)**	**'Independent' (%)**	**'Unclear' (%)**
EMA	ADHD	10	6 (60%)	4 (40 %)	0	0
EMA	Schizophrenia	7	5 (71 %)	2 (29 %)	0	0
EMA	Alcohol dependence	6	4 (67 %)	1 (17 %)	1 (17 %)	0
EMA	PTSD	5	4 (80 %)	0	1 (20 %)	0
EMA	Insomnia	5	3 (60 %)	2 (40 %)	0	0
EMA	Premenstrual dysphoric disorder	5	3 (60 %)	0	2 (40 %)	0
EMA subtotal		**38**	**25 (66 %)**	**9 (24 %)**	**4 (10 %)**	**0**
FDA	ADHD	7	2 (29 %)	3 (43 %)	0	2 (29 %)
FDA	Opioid substance disorder	3	2 (67 %)	0	0	1 (33 %)
FDA	Major depressive disorder	17	6 (35 %)	5 (29 %)	2 (12 %)	4 (24 %)
FDA	Alcoholism	5	3 (60 %)	1 (20 %)	0	1 (20 %)
FDA Subtotal		**32**	**13 (41 %)**	**9 (28 %)**	**2 (6 %)**	**8 (25 %)**
Total		70	38 (54 %)	18 (26 %)	6 (9 %)	8 (11 %)

Table 3. Stakeholder comments categorised by conflicts of interest

Regulator	Guideline	No. comments	'Industry' (%)	'Not-industry but with industry-related conflicts' (%)	'Independent' (%)	'Unclear' (%)
EMA	ADHD	187	153 (82 %)	34 (18 %)	0	0
EMA	Schizophrenia	214	171 (80 %)	43 (20 %)	0	0
EMA	Alcohol dependence	97	67 (69 %)	22 (23 %)	8 (8 %)	0
EMA	PTSD	66[a]	N/A	N/A	N/A	N/A
EMA	Insomnia	147	98 (67 %)	49 (33 %)	0	0
EMA	Premenstrual dysphoric disorder	39	28 (72 %)	0	11 (28 %)	0
EMA subtotal		**750 (684 assigned comments)**	**517 (76 %)***	**148 (22 %)***	**19 (3 %)***	**0**
FDA	ADHD	48	18 (38 %)	25 (52 %)	0	5 (10 %)
FDA	Opioid substance disorder	17	16 (94 %)	0	0	1 (6 %)
FDA	Major depressive disorder	151	59 (39 %)	67 (44 %)	17 (11 %)	8 (5 %)
FDA	Alcoholism	17	11 (65 %)	1 (6 %)	0	5 (29 %)
FDA Subtotal		**233**	**104 (45 %)**	**93 (40 %)**	**17 (7 %)**	**19 (8 %)**
Total		983 (917 assigned comments)	621 (68 %)*	241 (26 %)*	36 (4 %)*	19 (2 %)*

[a)] The comments were not assigned to the individual stakeholders. *Calculated as the proportion of assigned comments, not the total number of comments.

Table 4. Overview of commenting phases on regulatory guidelines

Guideline development steps	**EMA**	**FDA**
Announcement of concept/draft document	On the "Open consultations" website[22]	In the *Federal Journal*[24] and the "newly added Guidance Documents" website[25]
Time period for commenting on drafts	3 to 6 months	2 months
Announcement of final guideline	On the "Open consultations" website[22]	In the *Federal Journal*[24] and the "newly added Guidance Documents" website[25]
Time period for commenting on final guidelines	Always open for comments	Always open for comments
Active recruitment of stakeholders (on any step in the development)	Yes, according to guideline	Yes, but not necessarily
Who can comment on documents	Everybody can comment	Everybody can comment
Legislation	Procedure for European Union guidelines and related documents within the pharmaceutical legislative framework [20]	Code of Federal Regulation, title 21, part 10, section 10.115, Good guidance practices [23]

Supplement 1

Appendix

Kim Boesen, Peter C Gøtzsche, John PA Ioannidis. EMA and FDA psychiatric drug trial guidelines: Assessment of guideline development and trial design recommendations

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eMethods

Inclusion of drug regulatory agency guidelines

EMA Clinical Efficacy and Safety Guidelines

The EMA *Clinical Efficacy and Safety Guidelines* are available on EMA's website. We screened all guidelines archived under the tag "Nervous system" (https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-efficacy-safety/clinical-efficacy-safety-nervous-system).

FDA Guidance Documents

FDA makes available their *Guidance Documents* on the website (https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs). We screened all guidelines labelled with the tags: "drugs" (Product), "Clinical/Medical" (topic), and "Center for Drug Evaluation and Research" (FDA Organization).

FDA File Docket Summary

The *Docket's Management* is available from https://www.regulations.gov/. To access the Guidance Documents' Docket Folder Summaries, you click on the Docket ID number on the FDA website. We downloaded all available documents and comments on 5 February 2020.

Stakeholder comment documents

FDA Guidance Documents

We included all comments available on each Guidance Document's Docket File Summary submitted to the draft versions, notices of availability, and final guidelines.

Counting the number of comments in FDA documents

In contrast to EMA, which collects and uniformly presents the stakeholder comments in one document, FDA makes available the individual stakeholder comments in the form they were

submitted to the Agency. This leads to a great variability in the structure of the comments. To harmonise the data extraction, we applied these rules:

(1) The unit of analysis was one individual comment, which could be a section or paragraph, regarding one particular subject related to the draft or guideline.
(2) One comment could be spread over several paragraphs, provided it was related to the same issue.
(3) If the submitted comment consisted of one long paragraph with no clear separation in content, we counted this as one comment.
(4) We included initial "introductory" parts of the submitted material as a comment as well, since these "introductory" or "general overview comments" were also included from the EMA stakeholder documents. If a cover letter was accompanying a comment submitted to FDA, we tried to avoid double counting of such general comments.
(5) We did not count passages that were not related to the guideline itself, but were of more general character, such as descriptions of the submitting organisation or company in cover letters.
(6) If several comments were raised within the same box (it occurred in EMA's stakeholder documents) and EMA gave several responses, also within the same box, we counted the number of EMA responses as the number of raised comments.

Categorising stakeholders according to their conflicts of interest

We categorised the stakeholders as:
(1) *industry* (pharmaceutical companies, pharmaceutical associations, and other private companies)
(2) *not-industry but with industry-related conflicts* (organisations, associations or individuals with financial conflicts of interest related to pharmaceutical companies)
(3) *independent* (organisations, associations and individuals without conflicts of interest related to the pharmaceutical industry)
(4) *unclear financial relationship* (there was insufficient information to identify and/or categorise the stakeholder).

If the stakeholder was an association, academic society or similar, we searched for information related to the organisation's funding and disclosed conflicts of interest for board or executive members. To separate between "independent" and "not-industry but with industry-related conflicts" organisations and associations, we searched for information declared on their respective websites and in annual reports about funding from pharmaceutical companies. We also took into consideration industry sponsorships in relation to annual meetings and conferences, as substantial revenues can be gained through the hosting of such events by providing opportunities for industry to arrange "satellite educational symposia" and similar activities. We extracted all available information and made an overall assessment of the conflicts of interest.

For individual stakeholders we searched on Google and PubMed to identify the commenter. If we were able to identify the stakeholder, we extracted data on declared conflicts of interest from websites, published journal articles and searched the Open Payments Data (https://openpaymentsdata.cms.gov/) for disclosed information about received industry payments.

We categorised drug regulatory agencies as "independent" stakeholders. This classification could be contested considering that drug regulatory agencies get substantial revenues from pharmaceutical companies for processing and approving new drug applications.

Guideline development

Searching for information on websites related to internal procedures (FDA)
We searched for FDA Manual of Policies and Procedures (MAPPs) related to the Center for Drug Evaluation and Research (CDER) procedures on the development of Guidance Documents. We found 183 MAPPs specifically related to CDER (on 13 April 2020), available from: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-manual-policies-procedures-mapp.

Two of these MAPPs were relevant: “Developing and Issuing Guidance”, March 2005 (https://www.fda.gov/media/71702/download), and “Developing Indication-Specific Guidances”, November 2014 (https://www.fda.gov/media/71717/download).

Data extraction and analysis

One researcher identified the research guidelines and stakeholder comments, extracted outcome data, and looked up conflicts of interests. Another researcher was involved in case of doubt about the inclusion of guidelines, conflicts of interest categorisation, or stakeholder comments. We reported the total number of guidelines, year of publication, and version type; total number of guideline committee members on each guideline, and proportion of guideline committee members according to their declared conflicts of interest; total number of stakeholders, total number of stakeholder comments on each guideline, and the proportion of stakeholders and comments categorised as *industry*, *not-industry but with industry-related conflicts*, *independent*, and *unclear relationship*. We did not apply statistics on the analyses of the commenting phase and the description of the trial design recommendations.

eResults

FDA Guidance Documents

Excluded guidelines

We did not include these guidelines: “antidepressant drugs – clinical evaluation” (9/1/1977), antianxiety drugs – clinical evaluation” (9/1/1977), “hypnotic drugs – clinical evaluation” (9/1/1977), and “psychoactive drugs in infants and children – clinical evaluation” (3/2/1998). These documents were not made for a particular condition.

Guideline committee member lists

Summary of telephone meeting with FDA

31 March 2020 with Sudarshini Satchi, Branch Chief, Freedom of Information team.

Ms. Satchi informed us that:

1. FDA employees are not allowed to have conflicts of interests during their employment at the Agency.
2. Guidance documents are authored internally in the Agency by divisions or offices and not by individuals or sole authors. This is in contrast to the working procedure for the advisory committee guidance documents where external members are often invited to participate.
3. Since FDA employees are not allowed to have conflicts of interests and because Agency employees author the Documents without external input, the FDA is not in possession of conflict of interest disclosures related to the Guidance Documents.

We asked for written guidance on this and were referred to the CDER websites and MAPPs published on the development of Guidance Documents. See eMethods on how we identified the relevant MAPPs.

Guideline recommendations versus clinical context

eTable 1. Autism Spectrum Disorder

Trial characteristic	**EMA adopted guideline (2017)**	**FDA guideline**	**Clinical context**
Trial duration	Short-term: 12 weeks or longer (section 7.3) Long-term: Randomised withdrawal trial for long-term effects, duration not specified (section 7.4)		Autism spectrum disorder is described as a life-long condition in the guideline (EMA 2017, executive summary)
Psychiatric comorbidity	Exclusion of severe comorbidity (psychosis, uncontrollable epilepsy, visual or hearing impairments) (section 5.2)		According to the guideline, co-morbid symptoms such as anxiety, depression, seizures, attention deficit, aggressive behaviours and sleep disorders are common (EMA 2017, section 1.2)
Enriched design	Yes, wash-out of prior medication (section 7.3)		The guideline recognises that stop of pharmacological treatment may lead to rebound and/or withdrawal symptoms (EMA 2017, section 8.2.3)
Efficacy outcomes	Core symptoms and functional outcomes by measurement tools or rating scales Quality of life may be assessed (section 6)	No guideline	We found one systematic review through COMET by McConachie et al.[1] They concluded, *"Twelve tools were identified as having the strongest supporting evidence, the majority measuring autism characteristics and problem behaviour. The patchy evidence and limited scope of outcomes measured mean these tools do not constitute a 'recommended battery' for use. In particular, there is little evidence that the identified tools would be good at detecting change in intervention studies. The obvious gaps in available outcome measurement include well-being and participation outcomes for children, and family quality-of-life outcomes, domains particularly valued by our informants (young people with ASD and parents)".*[1]

eTable 2. Bipolar disorder

Trial characteristic	**EMA adopted guideline (2001)***	**FDA guideline**	**Clinical context**
Trial duration	Acute manic episodes: 3-4 weeks for short-term and 12 weeks for maintenance of effect (section 6.1) Major depressive disorder:	No guideline	According to the guideline, bipolar disorder is considered a chronic disorder (EMA 2001, introduction)

	6-8 weeks for short-term and 3-6 months for maintenance (section 6.3)		
Psychiatric comorbidity	Exclusion criteria related to psychiatric comorbidity not specified		Frequent comorbidity was not specified in the guideline
Enriched design	Yes, wash-out of "relevant medication" (section 6) including those with "anti-manic properties" (section 6.1)		The guideline specified that participants need to be off medication "for a substantial period of time because of possible rebound phenomena" (EMA 2001, section 6.1)
Efficacy outcomes	Symptom rating scales (section 4)		We found one study through COMET by Eyring et al.,[2] which was a survey of 22 patients. The most important outcomes were severe depression, severe mania, quality of life, work/school functioning and social functioning.[2]

**Note that we extracted the recommendations from the 2001 guideline, and not the 2016 concept paper since it did not contain specific recommendations.*

eTable 3. ADHD

Trial characteristic	**EMA adopted guideline (2010)**	**FDA draft guideline (2019)**	**Clinical context**
Trial duration	Short term: 6-12 weeks Long-term: 6 months trial, either as a placebo-controlled trial or randomised withdrawal trial (section 6.2.2)	In children, the effect on growth-change must be evaluated for 12-months. Not specified if randomised, placebo-controlled design (line 218) Not specified for adults	According to the guideline, ADHD is considered a chronic condition (EMA 2010, section 1).
Psychiatric comorbidity	Exclusion of any axis I disorder, severe comorbid depressive and anxiety symptoms, axis II disorder, substance abuse (section 4.2)	Not specified	Psychiatric comorbidity is "almost inevitable" in children and "only 30 % of cases are pure ADHD". In adults especially substance abuse, borderline and antisocial personality disorder are frequent (EMA 2010, section 1.3)
Enriched design	Yes, washout of relevant medication for ADHD (section 6.2.1)	Not specified	The guideline recognises that stop of pharmacological treatment may lead to rebound and/or withdrawal symptoms (EMA 2010, section 7.2.1)
Efficacy outcomes	Rating scales of ADHD symptoms and functional domains (section 5.1 and 5.2)	Rating scales (line 115) and "simulated workplace environment" for trials in adults (line 123)	We did not find relevant articles in the COMET database. Eiring et al.'s systematic review[3] of patient preferences included one study with ADHD patients by Glenngård et al.[4] This study surveyed 285 parents of children with ADHD, adolescents, and adults with ADHD

			about their treatment preferences. The surveyed adult ADHD patients preferred "function during morning and school/workday" over "function during late afternoon/evening" and "side effects".[4] Glenngård cited a qualitative study by Mühlbacher.[5] They surveyed 219 ADHD patients and family members and reported that "enabling social contacts", "no mood swings", and "duration of effect all day" were the most important outcomes.[5]

eTable 4. OCD

Trial characteristic	**EMA adopted guideline (2005)**	**FDA guideline recommendation**	**Clinical context**
Trial duration	Short term: 8 - 14 weeks (section 4.4.1) Long-term: minimum 6-months in a randomised withdrawal study with re-randomisation of responders (section 4.4.2)	No guideline	OCD is described as a chronic condition in the EMA guideline (EMA 2005, introduction)
Psychiatric comorbidity	Restrictions regarding psychotic illness, bipolar disorder, borderline personality disorder, social anxiety disorder, eating disorders, substance abuse disorder and depression. It was specified the population should be "pure" OCD (section 2.2)		The guideline describes that the rates of psychiatric comorbidity "range from 74 % to 85 %", including major depressive disorder, anxiety disorders, substance abuse and eating disorders (EMA 2005, section 1.1)
Enriched design	Yes, "concomitant psychotropic treatment should be washed out" (section 2.2)		The guideline recognises that stop of pharmacological treatment may lead to rebound and/or withdrawal symptoms (EMA 2005, section 5.2.1)
Efficacy outcomes	Rating scales of symptoms and functional outcomes Quality may be assessed (section 3.1 and 3.2)		Through COMET, we found one ongoing study[6] aiming to develop a standardised set of outcomes in children and young people. The systematic review by Eiring et al.[3] did not identify studies with OCD.

eTable 5. Depression

Trial characteristic	EMA adopted guideline (2013)	FDA draft guideline (2018)	Clinical context
Trial duration	Short term: 4-8 weeks (section 4.2.1) Long term: 6 months as randomised withdrawal trial (section 4.2.2). Placebo-controlled trials should be limited to around 6 weeks (section 4.2.1)	Short term: 6-8 weeks (line 149) Long term: 6 months as randomised withdrawal study (line 177)	EMA writes there is "large variance in the natural course of MDD" and that "the duration of an episode varies considerably and may be more (or less than 6 months" (EMA 2013, section 4.1.2) Described as "cyclical" in FDA guideline (FDA 2018, line 175)
Psychiatric comorbidity	Exclusion criteria not specified. Stated that depression with comorbid psychiatric symptoms is not the focus of the guideline (section 2)	"Avoid unnecessary restrictions of study population" to include a broad population with e.g. comorbidity (line 229)	Anxiety disorders, bipolar disorder and other axis I disorders are mentioned as comorbid diagnoses, although the frequencies are not specified (EMA 2013, section 2 and 4.1.3)
Enriched design	Yes, "relevant medication has to be washed out" (section 4.2.4.2)	Not specified	The EMA guideline recognises that stop of pharmacological treatment may lead to rebound and/or withdrawal symptoms (EMA 2013, section 4.5.3.11)
Efficacy outcomes	Rating scales of symptoms and global assessment or social functioning (section 4.2.3)	Symptom rating scales (line 240)	In COMET we identified one ongoing study to define a core outcome set for depression in adults.[7] The systematic review by Eiring et al.[3] included four studies and concluded that the ability to cope with daily activities were more important than depressive symptoms.

eTable 6. General Anxiety Disorder

Trial characteristic	EMA adopted guideline (2005)	FDA guideline recommendation	Clinical context
Trial duration	Short term: minimum 8 weeks (section IV, 2.1) Long term: 6 to 12 months as a randomised withdrawal study (section IV, 2.2)	No guideline	The EMA guidelines stated, "*The Epidemiologic Catchment Area (ECA) study found that the duration of DSM-III GAD was longer than five years in 40% of patients*" (EMA 2005, introduction)
Psychiatric comorbidity	Exclusion of comorbid major depression, depressive symptoms, other anxiety disorders, psychotic illness, bipolar disorder, axis II disorder, substance abuse (section II, 2)		Psychiatric comorbidity is "frequently associated", such as depression and other anxiety disorders (EMA 2005, introduction)

Enriched design	Yes, washout of "active agents" (section IV, 2.1)		The guideline recognises that stop of pharmacological treatment may lead to rebound and/or withdrawal symptoms (EMA 2005, section V.2)
Efficacy outcomes	Rating scales of anxiety symptoms, global assessment and/or functioning (section III, 1 and III, 2) Quality of life may be assessed (section III, 3)		We did not identify relevant studies in the COMET database, or in the systematic review by Eiring et al.[3]

eTable 7. Panic Disorder

Trial characteristic	**EMA guideline recommendation**	**FDA guideline recommendation**	**Clinical context**
Trial duration	Link to guideline did not work	No guideline	Link to guideline did not work
Psychiatric comorbidity	Link to guideline did not work		Link to guideline did not work
Enriched design	Link to guideline did not work		Link to guideline did not work
Efficacy outcomes	Link to guideline did not work		Link to guideline did not work

eTable 8. Social anxiety

Trial characteristic	**EMA adopted guideline (2006)**	**FDA guideline recommendation**	**Clinical context**
Trial duration	Short term: minimum 12 weeks (section 4.2.1) Long term: 6-12 months as a randomised withdrawal study (section 4.2.2)	No guideline	Described as a chronic condition (EMA 2006, section 4.2.2)
Psychiatric comorbidity	Exclusion of major depression, depressive symptoms, anxiety disorders, schizophrenia, bipolar disorder, substance abuse, axis II disorder (section 2.2)		Comorbidity is frequent, "50 to 80 % of clinical patients with SAD have at least one other mental disorder", including anxiety and depressive disorders (EMA 2006, section 1)
Enriched design	Yes, washout of "psychoactive compounds[s] with impact on SAD" (section 2.2 and 4.2.1)		The guideline recognises that stop of pharmacological treatment may lead to rebound and/or withdrawal symptoms (EMA 2006, section 5.2)
Efficacy outcomes	Rating scales of symptoms and global assessment (section 3.1 and 3.2) Quality of life may be		We did not identify relevant studies in the COMET database, or in the systematic review by Eiring et al.[3]

	assessed (section 3.3)		

eTable 9. Schizophrenia

Trial characteristic	EMA adopted guideline (2012)	FDA guideline recommendation	Clinical context
Trial duration	Short term: 6 weeks (section 4.4.3.3) Long term: Up to 6 months as a randomised withdrawal study or 12 months in non-inferiority active comparator trial (section 4.4.4). Or hybrid active-comparator trial (12 months) followed by randomised withdrawal (6 months) (section 4.4.4)	No guideline	Described as a chronic condition (EMA 2012, section 4.4.4)
Psychiatric comorbidity	Exclusion of psychiatric comorbidity to avoid confounding, but specific diagnoses not specified (section 4.4.3.2)		Schizophrenia is associated with manic and depressive symptoms, anxiety, OCD, substance abuse and personality disorders (EMA 2012, section 1.1)
Enriched design	Yes, "prior antipsychotics should be washed out" and "typically a few days will be appropriate for run-in" [of washing out the antipsychotics during a placebo run-in] (section 4.4.3.5)		The risk of withdrawal or rebound symptoms not specified in the guideline, but "withdrawal and dependence" symptoms should be assessed (EMA 2012, section 4.7.1)
Efficacy outcomes	Symptom rating scales (section 4.2.1)		Through COMET, we identified a protocol for the PARTNERS2 project by Keeley et al.[8] to develop core outcome sets for patients with bipolar and schizophrenia. The systematic review by Eiring et al.[3] included nine studies but reported ambiguous results regarding patient preferences, "Patients with schizophrenia tended to value disease states as higher and side effects as lower, compared to other stakeholder groups".[3]

eTable 10. Alcohol dependence

Trial characteristic	EMA adopted guideline (2010)	FDA draft guideline (2015)	Clinical context
Trial duration	Short term: 3-6 months	Minimum 6 months as an RCT (line 153 and	Described as a chronic condition (EMA 2010, executive summary)

	Long term: 12-15 months randomised withdrawal study of responders without treatment; or 12-15 months as an RCT (if new compound)[a] (section 4.3.3)	185)	
Psychiatric comorbidity	In general, comorbid disorders should be excluded Patients with "milder symptoms" may be included" (section 4.1.2.)	Comorbidity allowed, although it was not specified if it also applied to psychiatric comorbidity (line 242)	Psychiatric comorbidity is common, such as personality disorder and mood disorders (EMA 2010, introduction)
Enriched design	Not specified	Not specified	The risk of withdrawal or rebound symptoms not specified in the guidelines
Efficacy outcomes	Full abstinence or no heavy drinking (primary outcome) (section 4.2.1) 23 potential secondary outcomes listed depending on the primary outcome (section 4.2.2)	Full abstinence or no heavy drinking (line 155)	Through COMET we identified one consensus guideline about core outcome sets by Shorter et al.[9] They reported a ranking of 90 outcomes in five different domains. The systematic review by Eiring et al.[3] did not identify studies with alcohol dependence.

a) It was not clearly described how these trials should be designed and conducted.

eTable 11. PTSD

Trial characteristic	**EMA adopted guideline (2008)**	**FDA guideline**	**Clinical context**
Trial duration	Short term: 10-12 weeks Long-term: Randomised withdrawal trial design. Duration not specified (section 6)	No guideline	PTSD is described as a chronic condition (EMA 2008, section 6)
Psychiatric comorbidity	Restrictions regarding depression, other anxiety disorders, OCD, psychotic illness, bipolar disorder, axis II disorders, substance abuse (section 4)		Frequent comorbidity was not specified in the guideline
Enriched design	Yes, washout of "active agents" (section 6)		Rebound/withdrawal phenomena upon treatment stop are recognised in the guideline (EMA 2008, section 8)
Efficacy outcomes	Rating scales of symptoms and global		Through COMET, we identified one ongoing study[6] to define core

	assessment (section 5)		outcome sets for PTSD in children and adolescents. The systematic review by Eiring et al.[3] did not identify studies with PTSD.

eTable 12. Insomnia

Trial characteristic	EMA adopted guideline (2011)	FDA guideline	Clinical context
Trial duration	Short term: 2-4 weeks (section 6.2.1) Long term: Minimum 6 months double-blind RCT or (preferably) randomised withdrawal study (section 6.2.2)	No guideline	Described as great variability across life-span (EMA 2011, introduction)
Psychiatric comorbidity	New drugs preferably first tested in patients with primary insomnia and not secondary insomnia (insomnia as a symptom of other disorders) (section 4.2)		According to the guideline comorbid psychiatric disorders are frequent (EMA 2011, section 6.3)
Enriched design	Yes, "wash-out" of previous treatments (section 5.2.1)		Rebound/withdrawal phenomena upon treatment stop are recognised in the guideline (EMA 2011, section 8.1)
Efficacy outcomes	Self rated sleep quality and day-time functioning Polysomnography Quality of life (section 5.2.2)		Through COMET, we found one consensus statement[10] about core outcomes in children adolescents. The statement recommended polysomnography and actigraphy, and self reported sleep

eTable 13. Premenstrual dysphoric syndrome

Trial characteristic	EMA adopted guideline (2011)	FDA guideline	Clinical context
Trial duration	"6 cycles", i.e. 6 months (section 4.3.3) Long-term harms: minimum "12 cycles", study design not specified (section 4.5.4)	No guideline	Described as a chronic condition in the guideline (EMA 2011, section 1.1 and 4.3.3)
Psychiatric comorbidity	Restrictions regarding axis-I or substance abuse disorders (section 4.1.2)		Dysthymia, major depressive disorder, and anxiety disorders are the most common axis 1 comorbidities. Rates not specified

			(EMA 2011, section 1.5)
Enriched design	Yes, "relevant medication has to be washed out" (section 4.3.2)		Rebound and withdrawal phenomena after stop of pharmacological treatment is recognised in the guideline (EMA 2011, section 4.5.3)
Efficacy outcomes	Self-rated symptoms on rating scales (section 4.1.2) Psychological, physical and functional changes measured on rating scales (section 4.2.2)		Through COMET, we found one systematic review by Budeieri et al.[11] They assessed available symptom rating scales and concluded that a standardised outcome set is required. The systematic review by Eiring et al.[3] did not include studies with premenstrual dysphoric syndrome.

eTable 14. Opioid use disorder

Trial characteristic	**EMA guideline**	**FDA final guideline (2019)**	**Clinical context**
Trial duration	No guideline	Not specified	Natural course not specified in the guideline
Psychiatric comorbidity		Not specified	Frequent comorbidity not specified in the guideline
Enriched design		Yes, "history of previous drug product treatment for OUD is acceptable" (Section III, B, 1)	The risk of withdrawal or rebound symptoms not specified in the guideline
Efficacy outcomes		Responder rates of opioid use measured with urine toxicology (section III, B, 2) Applicant may propose other outcomes, such as "e.g., reduction in *craving*, improvement in sleep or mood, other patient-reported outcomes" (section 3, B, 3)	Through COMET, we identified one ongoing study[12] to establishing core outcomes for opioid misuse intervention trials. The systematic review by Eiring et al.[3] did not include studies of opioid abuse.

eTable 15. Low sexual interest, desire, and/or arousal in women

Trial characteristic	**EMA guideline**	**FDA draft guideline (2016)**	**Clinical context**
Trial duration	No guideline	24 weeks or more (line 115)	Natural course not specified in the guideline
Psychiatric comorbidity		Exclusion criteria "should be limited" to enable a representative sample of participants (line 173)	Frequent comorbidity not specified in the guideline. It is stated that psychiatric conditions can "cause of contribute to sexual dysfunction" (line 73)

Enriched design		Not specified	The risk of withdrawal or rebound symptoms not specified in the guideline
Efficacy outcomes		Number of self-reported satisfying sexual events and self rating of sexual interests, arousal and distress (line 370) It is stated that a patient-reported outcome (PRO) "is the most appropriate clinical outcome" (line 209)	Through COMET we found one consensus document.[13] They recommended self-reported scales of sexual functioning (primary) and satisfying sexual events, physiologic measures, partner assessments, and relationship satisfaction (secondary)

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13. Clayton AH, Dennerstein L, Fisher WA, et al. Standards for Clinical Trials in Sexual Dysfunction in Women: Research Designs and Outcomes Assessment. *J Sex Med* 2010;7:541-560.

Supplement 2

Regulatory correspondence

Kim Boesen, Peter C Gøtzsche, John PA Ioannidis. EMA and FDA psychiatric drug trial guidelines: Assessment of guideline development and trial design recommendations.

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Authors' note

We have included all relevant emails and correspondences with the agencies. We have not included courtesy and email exchanges that were irrelevant for this research project.

Stanford, California
10 February 2020

European Medicines Agency

Freedom of Information Act request

We are currently working on a research project related to EMA and FDA regulatory research guidelines on how to design pivotal psychiatric drug trials. The protocol for our project is available here: https://www.medrxiv.org/content/10.1101/2020.01.22.20018499v1.

As part of the project, we would like to assess the complete lists of guideline committee members and their declared conflicts of interest.

We would therefore like to file a Freedom of Information Act request for access to the committee member lists and their declared conflicts of interests for the following 13 EMA Clinical Efficacy and Safety Guidelines:

EMA clinical efficacy and safety guidelines:

- Clinical development of medicinal products for the treatment of autism spectrum disorder (ASD) (https://www.ema.europa.eu/en/clinical-development-medicinal-products-treatment-autism-spectrum-disorder-asd)
- Clinical investigation of medicinal products for the treatment and prevention of bipolar disorder (https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-treatment-prevention-bipolar-disorder)
- Clinical investigation of medicinal products for the treatment of attention deficit hyperactivity disorder (ADHD) (https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-treatment-attention-deficit-hyperactivity-disorder-adhd)
- Clinical investigation of medicinal products for the treatment of obsessive compulsive disorder (https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-treatment-obsessive-compulsive-disorder)
- Clinical investigation of medicinal products in the treatment of depression (https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-treatment-depression)
- Clinical investigation of medicinal products indicated for generalised anxiety disorder (https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-indicated-generalised-anxiety-disorder)
- Clinical investigation of medicinal products indicated for panic disorder (https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-indicated-panic-disorder)

- Clinical investigation of medicinal products indicated for the treatment of social anxiety (https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-indicated-treatment-social-anxiety)
- Clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia (https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-including-depot-preparations-treatment-schizophrenia)
- Development of medicinal products for the treatment of alcohol dependence (https://www.ema.europa.eu/en/development-medicinal-products-treatment-alcohol-dependence)
- Development of medicinal products for the treatment of post-traumatic stress disorder (https://www.ema.europa.eu/en/development-medicinal-products-treatment-post-traumatic-stress-disorder)
- Medicinal products for the treatment of insomnia (https://www.ema.europa.eu/en/medicinal-products-treatment-insomnia)
- Treatment of premenstrual dysphoric disorder (https://www.ema.europa.eu/en/treatment-premenstrual-dysphoric-disorder)

In the final paper, we will report the number of committee members and the proportion of committee members with declared conflicts of interest for each research guideline. We will not report individual information, such as committee member names or names of disclosed conflicts of interest.

Please contact me if our request needs further clarification.

Sincerely,

Kim Boesen, MD
Nordic Cochrane Centre

Freedom of Information Act request: EMA's Clinical and Efficacy Guidelines - ASK-67339

Garrido-Lestache Silvia <Silvia.Garrido@ema.europa.eu> Tue, Feb 11, 2020 at 4:09 PM
To: "kb@cochrane.dk" <kb@cochrane.dk>

Dear Mr Boesen ,

Thank you for your access to documents request which has been registered under reference number ASK-67339. However, before we can start processing it, we need to clarify its scope.

Your request reads as follows:

“We would therefore like to file a Freedom of Information Act request for access to the committee member lists and their declared conflicts of interests for the following 13 EMA Clinical Efficacy and Safety Guidelines… “

In order to process your request, we would like you to confirm that the documents requested are the following:

* List of committee members who develop each of the guidelines listed in the scope

* The Declaration of Interest (DoI) for all the members who develop each of the guidelines listed in the scope

Kindly confirm that our understanding is correct in order to start processing the request. I look forward to hearing from you soon.

Kind regards,

Silvia Garrido-Lestache

Access to Documents

Documents Access and Publication Service

Office of the Deputy Executive Director

European Medicines Agency

Classified as internal/staff & contractors by the European Medicines Agency

This e-mail has been scanned for all known viruses by European Medicines Agency.

Freedom of Information Act request: EMA's Clinical and Efficacy Guidelines - ASK-67339

Kim Boesen <kb@cochrane.dk> Tue, Feb 11, 2020 at 8:41 PM
To: Garrido-Lestache Silvia <Silvia.Garrido@ema.europa.eu>

Dear Silvia Garrido-Lestache,

Thank you very much for your email.

Yes, it is correctly understood that we are asking for 1) A list of committee members for each of the mentioned 13 guidelines, and 2) the declaration of interests for the committee members.

Thank you very much for your help. Please contact me if my request needs further clarification.

Sincerely,
Kim Boesen
[Quoted text hidden]
--
Kim Boesen, MD
Researcher
Nordic Cochrane Centre

[EMA Service Desk] (ASK-67339) Freedom of Information Act request: EMA's Clinical and Efficacy Guidelines

Poulimenou Despina (JIRA) <noreply@ema.europa.eu> Fri, Feb 14, 2020 at 3:27 PM
Reply-To: noreply@ema.europa.eu
To: kb@cochrane.dk

Re: EMA request reference ASK-67339

Dear Dr Boesen,

Thank you for your access to documents request.

Your request will be dealt in accordance with the principles and limits established in Regulation (EC) No 1049/2001 regarding public access to European Parliament, Council and Commission documents (the Regulation), as applicable to the European Medicines Agency (EMA) pursuant to Article 73 of Regulation (EC) No 726/2004.

Please note that EMA is currently operating within the fourth phase of its business continuity plan to ensure operational continuity during its relocation to Amsterdam. Whilst every effort is being made to process all requests as soon as possible, you should be aware that due to these exceptional circumstances from October 2019 requests cannot be processed immediately and will be dealt in a chronological order from the time they were received.

Please also note that we currently have in the system 3 requests to access documents from your firm.

As it concerns several documents, the principle set out in our policy states the Agency will apply the principle of proportionality in order to avoid the core business tasks of the Agency and its performance being jeopardised by the workload related to activities conducted by the Agency in accordance with the Regulation.

ASK-60717 will be processed first

ASK-65817 and ASK-67339 will be processed in turn one by one in this order.

Should you have any different priority order in processing them, please let us know (of note this email address is a “no-reply”) otherwise we will manage them as shown above ending with request ASK-67339.

You will be informed by an ATD coordinator when your procedure starts.

Thank you for considering the above.

Yours sincerely,
Despina Poulimenou
Documents Access and Publication Service
Stakeholders & Communication Division

European Medicines Agency
Domenico Scarlattilaan 6, 1083 HS Amsterdam, The Netherlands
Telephone: +31 (0)88 781 6000

Got a question? Ask EMA at www.ema.europa.eu/contact

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==========
Original Subject: Freedom of Information Act request: EMA's Clinical and Efficacy Guidelines
Original Description: Freedom of Information Act request We are currently working on a research project related to EMA and FDA regulatory research guidelines on how to design pivotal psychiatric drug trials. The protocol for our project is available here: https://www.medrxiv.org/content/10.1101/2020.01.22.20018499v1. As part of the project, we would like to assess the complete lists of guideline committee members and their declared conflicts of interest. We would therefore like to file a Freedom of Information Act request for access to the committee member lists and their declared conflicts of interests for the following 13 EMA Clinical Efficacy and Safety Guidelines: • Clinical development of medicinal products for the treatment of autism spectrum disorder (ASD) (https://www.ema.europa.eu/en/clinical-development-medicinal-products-treatment-autism-spectrum-disorder-asd) • Clinical investigation of medicinal products for the treatment and prevention of bipolar disorder (https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-treatment-prevention-bipolar-disorder) • Clinical investigation of medicinal products for the treatment of attention deficit hyperactivity disorder (ADHD) (https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-treatment-attention-deficit-hyperactivity-disorder-adhd) • Clinical investigation of medicinal products for the treatment of obsessive compulsive disorder (https://www.ema.europa.eu/en/clinical-

investigation-medicinal-products-treatment-obsessive-compulsive-disorder) • Clinical investigation of medicinal products in the treatment of depression (https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-treatment-depression) • Clinical investigation of medicinal products indicated for generalised anxiety disorder (https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-indicated-generalised-anxiety-disorder) • Clinical investigation of medicinal products indicated for panic disorder (https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-indicated-panic-disorder) • Clinical investigation of medicinal products indicated for the treatment of social anxiety (https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-indicated-treatment-social-anxiety) • Clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia (https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-including-depot-preparations-treatment-schizophrenia) • Development of medicinal products for the treatment of alcohol dependence (https://www.ema.europa.eu/en/development-medicinal-products-treatment-alcohol-dependence) • Development of medicinal products for the treatment of post-traumatic stress disorder (https://www.ema.europa.eu/en/development-medicinal-products-treatment-post-traumatic-stress-disorder) • Medicinal products for the treatment of insomnia (https://www.ema.europa.eu/en/medicinal-products-treatment-insomnia) • Treatment of premenstrual dysphoric disorder (https://www.ema.europa.eu/en/treatment-premenstrual-dysphoric-disorder) In the final paper, we will report the number of committee members and the proportion of committee members with declared conflicts of interest for each research guideline. We will not report individual information, such as committee member names or names of disclosed conflicts of interest. Please contact me if our request needs further clarification. Sincerely, Kim Boesen, MD Nordic Cochrane Centre

This e-mail has been scanned for all known viruses by European Medicines Agency.

29/06/2020

Subject of your enquiry:

RE: EMA request reference ASK-67570

Your question(s):

Dear Despina Poulimenou,

We submitted on 10 February 2020 a Freedom of Information Act request (ASK-67570) regarding access to the committee member lists and the corresponding declarations of interests related to 13 EMA Clinical Efficacy and Safety guidelines.

We were informed by you on 14 February that our request was placed in queue.

We would like to know the status for our request and when we can expect to receive the requested information?

Sincerely,
Kim Boesen, MD
Nordic Cochrane Centre

AskEMA - Response to ASK-71136 - RE: EMA request reference ASK-67570

1 message

AskEMA No-Reply <AskEMA.noreply@ema.europa.eu> Tue, Jun 30, 2020 at 5:11 PM
To: kb@cochrane.dk

Dear Dr Boesen,

Thank you for your message regarding the status of your request ASK-67339.

As communicated in our email of 14 February 2020, EMA is currently operating within the fourth phase of its business continuity plan to ensure operational continuity during its relocation to Amsterdam. Whilst every effort is being made to process all requests as soon as possible, from October 2019 requests cannot be processed immediately and are dealt in a chronological order from the time they were received.

This message is also publicly available on the access to documents online form page: https://www.ema.europa.eu/en/about-us/contact/send-question-european-medicines-agency.

Please rest assured that we are processing all the requests for access to documents in the queue in the order in which they were received. Because your request is still in the queue, you have not received notification that we have started processing it.

At this point in time the Agency cannot confirm any specific timelines for processing your request but when it is removed from the queue and we start dealing with it, you will receive an acknowledgement from the access to documents coordinator to whom it has been assigned.

In addition, as previously communicated, please note that we have in the system other requests from your organisation that were submitted before ASK-67339 and are currently being processed. Consequently, your request cannot be removed from the queue until the ongoing requests have been finalised.

Thank you for considering the above.

Yours sincerely,
Despina Poulimenou
Documents Access and Publication Service
Stakeholders and Communication Division

European Medicines Agency

Domenico Scarlattilaan 6, 1083 HS Amsterdam, The Netherlands
Send us a question. Go to www.ema.europa.eu/contact Telephone: +31 (0)88 781 6000

We received your question(s) on: **29/06/2020**

Subject of your enquiry: **RE: EMA request reference ASK-67570**

Your question(s):
Dear Despina Poulimenou,

We submitted on 10 February 2020 a Freedom of Information Act request (ASK-67570) regarding access to the committee member lists and the corresponding declarations of interests related to 13 EMA Clinical Efficacy and Safety guidelines.

We were informed by you on 14 February that our request was placed in queue.

We would like to know the status for our request and when we can expect to receive the requested information?

Sincerely,
Kim Boesen, MD
Nordic Cochrane Centre

This e-mail has been scanned for all known viruses by European Medicines Agency.

Cochrane Nordic

Trusted evidence. Informed decisions. Better health.

Nordic Cochrane Centre
Rigshospitalet, Dept. 7811
Blegdamsvej 9
2100 Copenhagen Ø, Denmark
Tel: +45 35 45 71 12
E-mail: general@cochrane.dk
www.nordic.cochrane.org

Copenhagen, Denmark
10 February 2020

US Food and Drug Administration

Freedom of Information Act request

We are currently working on a research project related to EMA and FDA regulatory research guidelines on how to design pivotal psychiatric drug trials. The protocol for our project is available here: https://www.medrxiv.org/content/10.1101/2020.01.22.20018499v1.

As part of the project, we would like to assess the complete lists of guideline committee members and their declared conflicts of interest.

We would therefore like to file a Freedom of Information Act request for access to the committee member lists and their declared conflicts of interests for the following five FDA Guidance Documents.

FDA Guidance Documents:

- Attention Deficit Hyperactivity Disorder: Developing Stimulant Drugs for Treatment Guidance for Industry (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/attention-deficit-hyperactivity-disorder-developing-stimulant-drugs-treatment-guidance-industry)

- Opioid Use Disorder: Developing Depot Buprenorphine Products for Treatment (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/opioid-use-disorder-developing-depot-buprenorphine-products-treatment)

- Major Depressive Disorder: Developing Drugs for Treatment (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/major-depressive-disorder-developing-drugs-treatment)

- Low Sexual Interest, Desire, and/or Arousal in Women: Developing Drugs for Treatment Guidance for Industry (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/low-sexual-interest-desire-andor-arousal-women-developing-drugs-treatment-guidance-industry)

- Alcoholism: Developing Drugs for Treatment (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/alcoholism-developing-drugs-treatment)

In the final paper, we will report the number of committee members and the proportion of committee members with declared conflicts of interest for each Guidance Document. We will not report individual information, such as committee member names or names of disclosed conflicts of interest.

Please contact me if our request needs further clarification.

Sincerely,

Kim Boesen, MD
Nordic Cochrane Centre
Rigshospitalet, Dept. 7811
2100 Copenhagen Ø
Denmark
+45 35 45 71 12
kb@cochrane.dk

FDA Receipt of FOI Request

FDA_FOI@fda.gov <FDA_FOI@fda.gov> Mon, Feb 24, 2020 at 3:10 PM
To: kb@cochrane.dk

Nordic Cochrane Centre Kim Boesen

Re: Confirmation # FDA2062748
Requester Ctrl #:
In Reply refer to: 2020-1608

The Food and Drug Administration (FDA) has received your Freedom of Information Act (FOIA) request for records regarding:

committee members lists and their declared conflicts of interest for five FDA Guidance Documents

We will respond as soon as possible and may charge you a fee for processing your request. If your informational needs change, and you no longer need the requested records, please contact us to cancel your request, as charges may be incurred once processing of your request has begun. For more information on processing fees, please see http://www.fda.gov/RegulatoryInformation/FOI/FOIAFees/default.htm.

Due to an increase in the number of incoming requests, we may be unable to comply with the twenty-working-day time limit in this case, as well as the ten additional days provided by the FOIA. The actual processing time will depend on the complexity of your request and whether sensitive records, voluminous records, extensive search, and/or consultation with other HHS components or other executive branch agencies are involved. Please note that requests for medical device approval records (e.g. 510K, PMA, DEN) may take up to 18 to 24 months to process.

If you have any questions about your request, please call Rochelle A. Coleman, Information Technician at 301-796-8982 or write to us at:

Division of Freedom of Information,
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1050
Rockville, MD 20857
Fax: 301-827-9267

You also have the right to seek dispute resolution services from:

FDA FOIA Public Liaison
Office of the Executive Secretariat
5630 Fishers Lane, Room 1050
Rockville, MD 20857
E-Mail: FDAFOIA@fda.hhs.gov

and/or:

Office of Government
Information Services
National Archives and Administration
8601 Adelphi Road - OGIS
College Park, MD 20740-6001
Telephone: 202-741-5770
Toll-Free: 1-877-684-6448
E-Mail: ogis@nara.gov
Fax: 202-741-5769

Note: Do NOT reply directly to this E-mail

RE: Your FOIA request

Satchi, Sudarshini (Darshini) <Sudarshini.Satchi@fda.hhs.gov> Mon, Mar 23, 2020 at 9:40 PM
To: "kb@cochrane.dk" <kb@cochrane.dk>

Hello,

We have received your FOIA request. Please let me know if there is a time this week that we can discuss your request. Thank you.

Darshini Satchi

Branch Chief FOI Team

Division of Information Disclosure Policy

CDER

301-796-3496

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Paper 4

How many clinical trials are missing when drug regulators make decisions? A case study of extended-release methylphenidate for ADHD in adults

Kim Boesen,[1] Karsten Juhl Jørgensen,[1] Peter C Gøtzsche[2]

[1]Nordic Cochrane Centre, Rigshospitalet Dept. 7811, Copenhagen, Denmark

[2]Institute for Scientific Freedom, Copenhagen, Denmark

Submitted for publication

GRADUATE SCHOOL OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

PHD-THESIS
DECLARATION OF CO-AUTHORSHIP

The declaration is for PhD students and must be completed for each conjointly authored article. Please note that if a manuscript or published paper has ten or less co-authors, all co-authors must sign the declaration of co-authorship. If it has more than ten co-authors, declarations of co-authorship from the corresponding author(s), the senior author and the principal supervisor (if relevant) are a minimum requirement.

1. Declaration by	
Name of PhD student	Kim Boesen
E-mail	kb@cochrane.dk
Name of principal supervisor	Jacob Rosenberg
Title of the PhD thesis	Methodological limitations in psychiatric drug trials with a particular focus on extended-release methylphenidate

2. The declaration applies to the following article	
Title of article	How many clinical trials are missing when drug regulators make decisions? A case study of extended-release methylphenidate for ADHD in adults
Article status	
Published ☐ Date:	Accepted for publication ☐ Date:
Manuscript submitted ☒ Date: 21 May 2020	Manuscript not submitted ☐
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	

3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD-student's contribution to the article **A**. Has essentially done all the work (> 90 %) **B**. Has done most of the work (60-90 %) **C**. Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
1. Formulation/identification of the scientific problem	A
2. Development of the key methods	A
3. Planning of the experiments and methodology design and development	A
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	A
5. Conducting the analysis of data	A
6. Interpretation of the results	A
7. Writing of the first draft of the manuscript	A
8. Finalisation of the manuscript and submission	A
Provide a short description of the PhD student´s specific contribution to the article.[i] Coining the idea for the project, collecting data, corresponding with drug regulatory agencies, analysing data, writing first daft, revising and finalising manuscript.	

4. Material from another thesis / dissertation[ii]	
Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?	Yes: ☐ No: ☒
If yes, please state name of the author and title of thesis / dissertation.	
If the article is part of another author's academic degree, please describe the PhD student´s and the author´s contributions to the article so that the individual contributions are clearly distinguishable from one another.	

5. Signatures of the co-authors[iii]

	Date	Name	Title	Signature
1.	3/7/20	Karsten Juhl Jørgensen	DSci	
2.	3/7/20	Peter C Gøtzsche	DSci	
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				

6. Signature of the principal supervisor

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 3/7/20
Principal supervisor: Jacob Rosenberg

7. Signature of the PhD student

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 3/7/20
PhD student: Kim Boesen

Please learn more about responsible conduct of research on the Faculty of Health and Medical Sciences' website.

[i] This can be supplemented with an additional letter if needed.

[ii] Please see Ministerial Order on the PhD Programme at the Universities and Certain Higher Artistic Educational Institutions (PhD Order) § 12 (4):

"Any articles included in the thesis may be written in cooperation with others, provided that each of the co-authors submits a written declaration stating the PhD student's or the author's contribution to the work."

[iii] If more signatures are needed please add an extra sheet.

How many clinical trials are missing when drug regulators make decisions? A case study of extended-release methylphenidate for ADHD in adults

Kim Boesen,[1] Karsten Juhl Jørgensen,[1] Peter C Gøtzsche[2]

[1]Nordic Cochrane Centre, Rigshospitalet Dept. 7811, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark

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Abstract: 323
Manuscript: 3000
References: 25

Abstract

Importance

It is unknown If drug regulatory agencies see all available evidence when they decide on new drugs.

Objectives

To assess whether drug regulatory agencies decided on applications for extended-release methylphenidate for use in adults with attention deficit hyperactivity disorder (ADHD) based on a select sample of trials.

Design

Cross-sectional study.

Setting

Publicly available regulatory documents.

Main outcomes and measures

We constructed an index of clinical trials of methylphenidate for ADHD in adult by cross-referencing trial registries, databases of published reports, and publicly available regulatory documents. We compared the clinical trials used by drug regulators in the United States, Australia, Canada, and Europe to approve methylphenidate for adult ADHD. We assessed whether applicants are required to submit all available clinical trials when they apply for market authorisation.

Results

We identified 18 extended-release methylphenidate trials (16 industry-sponsored, two publicly funded with industry involvement) of six different drug formulations. We found regulatory documents related to 12 drug applications (ten approved, two rejected) published by the US Food and Drug Administration (FDA) (three applications), Health Canada (three), the Australian Therapeutic Goods Administration (TGA) and the British Medicines and Healthcare products Regulatory Agency (two each), the Dutch Medicines

Evaluation Board and the German Bundesinstitut für Arzneimittel und Medizinprodukte (one each). There were trials missing in seven of the twelve regulatory documents (range one to six trials). The proportion of missing trial participants ranged from 14 % to 72 %. The FDA, the TGA, Health Canada and the European Medicines Agency all state in their submission requirements that all trials must be included in new drug applications, but ambiguous wording makes the requirements prone to interpretation.

Conclusion

Based on publicly available regulatory documents, seven of twelve regulatory decisions regarding extended-release methylphenidate for adult ADHD were made on a select sample of clinical trials. Current requirements seem to state that all available trials should be submitted in drug applications.

Registration

It is an exploratory analysis of this project: https://doi.org/10.1002/14651858.CD012857.

What is new?

What is already known on this topic

- Drug regulatory agencies base their decisions on clinical trials submitted by pharmaceutical companies
- Little is known whether drug regulators are missing evidence and make decisions based on select samples of trials

What this study adds

- It was not clear from publicly available documents which trials drug regulators based their decisions on to approve or reject new drugs
- Drug regulatory agencies were missing clinical trials in seven of twelve regulatory decisions regarding extended-release methylphenidate for adult ADHD
- Current regulatory submission requirements stipulate that applicants must submit all available trials, but ambiguous wording make them prone to interpretation

Background

Selective publication of trials[1, 2] and selective outcome reporting [3, 4] are common. For clinical trials published in medical journals, there can be important discrepancies compared to the raw trial data submitted to the drug regulators [5, 6, 7] and patient-centred outcomes and harms seem to be particularly underreported in published reports.[8, 9]

It was reported in 2008 that 31 % of antidepressant trials included in new drug applications submitted to the US Food and Drug Administration (FDA) were never published in medical journals.[10] Most of these unpublished trials did not favour the antidepressant and were considered "negative" by the FDA.[10] The authors assumed that FDA's cohort of clinical trials was exhaustive, but the authors did not investigate whether the companies had conducted more clinical trials.

When pharmaceutical companies apply for marketing authorisation of a new drug, they must submit an application in the form of a Common Technical Document.[11] It is the international standard for all major drug regulatory agencies, and it must contain information regarding quality assurance, non-clinical studies, e.g. pharmacokinetic and toxicology studies, and clinical trial data submitted in the form of clinical study reports.[12, 13]

Comparative studies have found that clinical study reports of antidepressant trials obtained from the European Medicines Agency (EMA)[14] and the UK regulator, Medicines and Healthcare products Regulatory Agency (MHRA), were incomplete [15, 16] and internally inconsistent.[17] In a systematic review of neuraminidase inhibitors for influenza based on clinical study reports,[5] it was noted that the EMA and FDA did not assess the largest oseltamivir trial during the approval procedure. To our knowledge, it has never been systematically assessed whether drug regulatory agencies may be missing entire clinical trials when they make decisions. Clinical study reports are generally not easily accessible, but most drug regulatory agencies make public documents available about their approved drugs.[18] We wanted to systematically assess if drug regulatory agencies: (1) transparently report which trials they based their decisions on; (2) may be missing entire clinical trials

when they make decisions; and (3) have specific submission requirements that mandate the applicants to submit all trials in new drug applications. We used a cohort of regulatory documents obtained for a systematic review of extended-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults.[19]

Methods

Index of published and registered clinical trials

For our systematic review of extended-release methylphenidate for ADHD in adults,[19] we systematically searched and cross-referenced databases of published reports, trial registries, pharmaceutical trial databases, corresponded with trial authors and searched for drug regulatory documents to create an index of extended-release methylphenidate trials. For this analysis, we were interested in clinical trials sponsored by pharmaceutical companies or publicly funded trials with industry-involvement. Purely publicly funded trials are rarely basis for new drug applications. We based our assessment of industry-involvement in publicly funded trials on the acknowledgement sections of published reports and on declarations of collaboration and/or industry sponsorships in trial registry entries.

Publicly available drug regulatory documents

We manually searched drug regulatory databases of publicly available documents[19] to identify regulatory documents related to new drug applications of methylphenidate: The FDA's database of Drug Approval Packages, the Australian Therapeutic Goods Administration's (TGA) Drug Product Database, Health Canada's Drug Product Database, EMA's database of Public Assessment Reports, and national European drug regulatory agency databases. See eMethods for details.

Missing trials in regulatory documents

We assessed each regulatory document and extracted information on the included clinical trials. We categorised the trials as *pivotal* (i.e. the main trials used for approval) or *other* (any kind of supporting trial appearing in the document).

We cross-referenced the index of trials with those trials identified in the regulatory documents. We categorised any indexed trial absent from the regulatory documents as "missing" if the trial was either ongoing or complete at the time of decision-making, and (1) the trial was sponsored by the pharmaceutical company that had applied for drug approval, or (2) it was a publicly funded trial with industry-involvement, e.g. the company had been involved with trial design, data collection or other aspects of trial conduct.

Regulatory requirements for new drug applications

We searched the FDA, the TGA, Health Canada, and the EMA websites to assess whether the agencies had stipulated specific requirements regarding submission of all available trial evidence. We did not search agencies in the individual European countries, since the drug approval standards are harmonised in the European Union. We asked the agencies to clarify any uncertainties in the publicly available documents and to specify whether submission of data from all existing trials, regardless of sponsorship, results and status of the trial, was required for the drug approval process.

Results

Index of published and registered trials

We identified 16 industry-sponsored trials and 2 publicly funded trials with industry involvement testing six different extended-release methylphenidate formulations: Osmotic-controlled release oral delivery system (OROS) methylphenidate marketed by Janssen as Concerta (10 trials), extended-release (ER) methylphenidate marketed by Medice as Medikinet (three trials), controlled-release (CR) methylphenidate marketed by Purdue as Foquest or Adhansia (two trials), CR methylphenidate marketed by Purdue as Biphentin (one trial), long-acting (LA) methylphenidate marketed by Novartis as Ritalin LA (one trial), and dex-methylphenidate marketed by Novartis as Focalin (one trial) (table 1). All trials assessed benefits and harms. Twelve trials had similar trial characteristics and six trials had particular trial design features: Reimherr 2004 and Jain 2003 used a cross-over design; Chronis-Tuscano 2004 included women with ADHD who also had daughters with ADHD; Winhusen 2005 (publicly-funded with industry involvement) also assessed smoking-

cessation related outcomes; Compas 2007 (publicly-funded with industry involvement) used a factorial design to also assess the impact of clinical management or specific group psychotherapy; and the Foquest Work 2014 trial used a simulated work environment in a cross-over trial. We have described key trial characteristics (eTable 2) and the time of registration in a trial registry and first publication (eTable 3).

Publicly available drug regulatory documents

We included drug regulatory documents related to twelve drug applications (table 2) from these agencies: The FDA (three applications), Health Canada (three), the TGA (two), MHRA (two), the Dutch Medicines Evaluation Board (MEB) (one) and the German Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) (one). Ten applications were approved and two were rejected (OROS methylphenidate by MHRA and long-acting methylphenidate by MEB).

The documents varied in length, detail, and trial data reporting. FDA's Approval Packages reported detailed results and summaries of the scientific discussions, whereas Health Canada's and the TGA's available documents reported sparse clinical trial data and did not include scientific discussions. The Public Assessment Reports published by the European National Competent Authorities (NCAs) varied in length and content from MHRA's 130-page report to BfArM's 7-page Public Assessment Report. We have described key document characteristics in eTable 4.

We contacted five regulatory agencies (FDA, TGA, Health Canada, BfArM, and MHRA) for clarifications regarding the applications. All five agencies partially responded and did not directly address our questions about the missing trials. Health Canada sent us Module 2.7 from the Clinical Study Report, which contains a list of all clinical trials submitted as part of the application. The other four agencies asked us to request specific documents from the Common Technical Document, such as particular modules from the Clinical Study Reports. See summary in eTable 5 and the full correspondence in Supplement 2.

Missing trials in regulatory documents

In seven of the twelve regulatory documents we identified missing trials, and the number of missing trials ranged from one to six (Figure 1). We illustrated the included and missing trials in Figure 1 where the size of each bar corresponds to the trials' sample sizes. See a tabulated list of included and missing trials in eTable 6. The proportion of missing trial participants ranged from 14 % for Health Canada's approval of CR methylphenidate to 72 % for Health Canada's approval of OROS methylphenidate (Table 3).

We have described each drug regulatory document and the decision about approval or rejection in detail in the supplement (eCase 1 to eCase 12). In Box 1, we summarise two cases to illustrate the possible impact of missing trials (Case 1), and how a pharmaceutical company was involved in a publicly funded trial but did not include it in the original application submission (Case 2).

----------Box 1----------

Case 1. FDA's internal disagreement regarding the approval of OROS methylphenidate

FDA's medical reviewer raised concerns about the drug's harms when he assessed the two pivotal clinical trials (Medori 2005 and Adler 2006) included in the application, particularly the cardiovascular safety. He recommended the conduct of a third trial as a condition for approval. The FDA Team Leader and the Division Director did not agree, among other reasons, because they believed it was not feasible, nor ethical, to conduct more clinical trials. The Division Director, Thomas Laughren stated, "The study proposed by Dr. Mannheim is simply not feasible. It would need to involve hundreds of thousands of patients, would need a placebo arm, and would take years to complete. In the meantime, the labels for Concerta and other drugs in this class already have very strong warning language that alerts prescribers to possible cardiovascular risks. Thus, I do not agree with the need for the study proposed by Dr. Mannheim, and I will not suggest it to the sponsor" (FDA review, p. 43 of 456). At the time of decision-making, five clinical trials were ongoing or completed that did not appear from the FDA Medical Office Review (Figure 1). We further note that the applicant submitted information regarding the existence of four placebo-controlled trials, but as stated in the FDA Medical Office Review, the Agency did not ask for

these trials, "The source papers have not been reviewed at the time of this review" (FDA review, p. 125 of 456). See details in eCase 1.

Case 2. BfArM's approval of extended-release methylphenidate and the Compas 2007 trial

The German drug regulator, BfArM, approved the drug for use in adults in April 2011 on the basis of two pivotal trials (Rösler 2004, Retz 2008) sponsored by the applicant, Medice. The trials were conducted between 2004 and 2006, and 2008 and 2010, respectively. A third, publicly funded trial, Compas 2007, was conducted in the same time period (2007 – 2011) and finished some months after BfArM's approval in August 2011. The Marketing Authorisation Holder, Medice, was involved in COMPAS' trial design and outcome collection. The Compas 2007 trial did not appear from the public assessment report summary and we asked BfArM whether they were informed about the COMPAS trial prior to approval. BfArM responded, *"At that time the COMPAS study had still been running (recruitment end 31 October 2011) and results could not be submitted"*. BfArM informed us that Medice included data from COMPAS in a type II variation submission, DE/H/0690/004-010/II/043/G, which was an expansion of the original indication to also include initiation of treatment in adults that have not previously been treated. The type II variation was approved in November 2017. The Compas 2007 trial included more participants and lasted significantly longer (52 weeks), compared to the two Medice-sponsored trials of 24 and 8 weeks, respectively. See details in eCase 5.

----------End of Box 1 ----------

Regulatory requirements for new drug applications

We have summarised the submission requirements from the four regulatory agencies, FDA, TGA, Health Canada and the EMA in Table 4.

The FDA guideline regarding New Drug Application submission requirements and the American legislation, the Code of Federal Regulation, specified that all clinical trials *pertinent* to the proposed indication should be included in the drug application. Similarly, the EMA guideline describing the content of the Common Technical Document specified

that all *pertinent* data should be submitted. The old EU Directive 2001/83, which forms the legal basis for the Marketing Authorisation Dossier, was more ambiguous and stated, "*all clinical trials should be communicated*". The TGA has adopted the European standard for the Common Technical Document. Health Canada requires applicants to attest a submission certificate stating, "*all pivotal trials necessary to support the proposed indications… have been provided*". See the verbatim statements in eTable 7.

Discussion

Summary of general findings

This may be the first report that systematically investigated whether drug regulatory agencies make decisions based on a select sample of clinical trials rather than all available trials. We identified missing trials in seven of our cohort of twelve publicly available drug regulatory documents. In the oseltamivir review for influenza,[5] the authors noted that the EMA and FDA approved the drug on select samples of trials and were missing the largest oseltamivir trial. We have made similar findings in our cohort of regulatory documents for methylphenidate for ADHD in adults. This raises concern that we may be dealing with a general problem rather than isolated cases.

There may be several explanations for the missing clinical trials. First, the companies deliberately do not include all trials in their applications. Second, the drug regulatory agencies do not unequivocally request that the applicants submit all trials. Third, the agencies do no conduct their own systematic searches of clinical trial registries and databases of published literature but rely on the material submitted by the applicant. Fourth, the agencies apparently do not always check that everything listed in the index has been submitted. Our research group have previously found that appendices were included in 32 of 70 trials of antidepressants,[15] and in Case 1, FDA noted they had not reviewed all bibliographic references submitted by the applicant. Although the submission requirements seem to stipulate that all available evidence should be submitted, the devil may lie in the detail. In the FDA, EMA (and subsequently TGA) guidelines, the required submitted material is labelled "pertinent" whereas Health Canada's submission certificate more directly addresses it as "all pivotal trials" (table 4). Whether this means that all data from all

available trials must be submitted, or only those trials that the regulatory agency and the applicant have already agreed on as part of the drug development program, is unclear.

We noted that the drug regulatory agencies did not directly address our questions regarding the extent of missing evidence; rather, they asked us to request specific documents, e.g. clinical study reports. Health Canada was the exception and provided the clinical study report Module 2.7 and fully addressed our questions. We understand that regulatory staff does not have authority or insight to explain former decisions. However, our questions regarding the availability of specific trials prior to decision-making were concrete and seem to constitute basic information that should already be in the public domain.

Limitations

It is important to reiterate that our analysis was based on publicly available documents and, except Health Canada's approval of OROS methylphenidate, we do not know whether the drug agencies had access to more data. Based on the one Module 2.7 we received from Health Canada, it seems that all pivotal trials may appear from the public documents. We would need access to those modules from all drug applications to confirm our results, which could take years to obtain. Since our findings were mainly limited to publicly available documents, this may on the other hand be an indicator of the level of transparency in the current system.

It is important to highlight the variation in the structure, content and disclosed material in the different documents. FDA's drug reviews and the European Public Assessment Reports are lengthy documents with detailed discussions of the included trials. The Canadian Product Monographs and the Australian Prescriber Information are summaries of product characteristics and not scientific reports. TGA and Health Canada also publish Public Assessment Reports, (called Summary Basis of Decision documents by Health Canada) but we did not identify any of relevance for this project.

The small sample of twelve drug applications is a limitation. It may be difficult to generalise across indications, fields, and drug regulators. We also do not know if we have missed additional rejected applications. It is not common to make assessment reports of rejected

drugs publicly available, e.g. as a principle the FDA does not do that, and we were surprised to find public assessment reports related to two rejected applications.

We may have missed some publicly funded trials with industry-involvement. Selective reporting of publicly funded trials is particularly pronounced,[20, 21] and sometimes the industry-involvement has not been declared in publications, even when the trial was later used in a registration application.[22]

Suggestions for improvements

We identified limitations in the current drug regulatory system with potentially serious consequences for the reliability of drug approvals. Despite our lengthy investigation, we are still not certain on what basis most drugs were approved. It is therefore regrettable that the FDA plans to weaken transparency by phasing out the publication of individual medical, statistical and other reviews and substituting them with less informative "integrated reviews".[23]

Drug regulators need to ensure that their decisions are based on all data from all relevant trials and not just a selection of them, whether or not the industry was involved. The current gaps could be addressed on several levels: (1) It would be highly recommendable that the agencies conduct their own systematic searches of trial registries and databases of published literature. According to FDA's internal guideline[24] (section 9.1) on how to conduct clinical reviews, the reviewers are currently not obliged to systematically search for evidence, "When performed, a comprehensive review of the literature can be included here"; (2) The current submission requirements need to be clarified to avoid loopholes and these requirements must be enforced; (3) The pharmaceutical companies need to be held accountable if they fail to submit relevant data or trials, or fail to inform about ongoing and planned trials; (4) It would be sensible to increase collaboration between regulatory agencies. Health Canada and the TGA have already initiated projects to increase transparency and openness, such as a collaborating on shared drug review assessments with the Singaporean and Swiss authorities.[25]

Conclusion

Based on publicly available regulatory documents, we found that seven of twelve regulatory decisions regarding extended-release methylphenidate for adult ADHD were made on a select sample of clinical trials, although current requirements seem to state that all available trials should be submitted in drug applications.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

All data underlying this project are available from, or referred to, in the supplements. It was an exploratory analysis related to our systematic review, and we have not published a separate protocol for this project.

Competing interests

None.

Funding

The study was not funded.

Author contributions

KB coined the idea, collected the data, drafted the letters to the drug regulators, and wrote the first draft of the paper. KJ and PCG supervised the correspondence with the drug regulators and critically revised the manuscript. All authors approved the final manuscript. KB is the guarantor and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Acknowledgements

None.

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Table 1. Index of extended-release methylphenidate trials for ADHD in adults with industry sponsorship or industry-involvement

Trial (registry ID)	**Formulation**	**Study start - stop**	**Sponsor**	**Industry-involvement**
Biederman 2003 (NCT00181571)	OROS methylphenidate	June 2003 – Aug 2007	McNeil and Janssen[a]	Industry trial
Jain 2003 (not registered)	Controlled-release methylphenidate	Oct 2003 – April 2004	Purdue	Industry trial
Reimherr 2004 (not registered)	OROS methylphenidate	Aug 2004 – Dec 2005	McNeil (funded in part)	Industry trial
Chronis-Tuscano 2004 (NCT00318981)	OROS methylphenidate	Dec 2004 – Dec 2006	McNeil[b]	Industry trial
Medori 2005 (NCT00246220)	OROS methylphenidate	Mar 2005 – Nov 2006	Janssen	Industry trial
Winhusen 2005 (NCT00253747)	OROS methylphenidate	Nov 2005 – Mar 2008	University of Cincinatti	Ortho-McNeil Janssen listed as collaborator[c]
Adler 2006 (NCT00326391)	OROS methylphenidate	Apr 2006 – Dec 2006	Janssen	Industry trial
Casas 2008 (NCT00714688)	OROS methylphenidate	Feb 2008 – Apr 2009	Janssen	Industry trial
Weisler 2009 (NCT00880217)	OROS methylphenidate	May 2009 – Jan 2010	Janssen	Industry trial
Goodman 2009 (NCT00937040)	OROS methylphenidate	July 2009 – Feb 2010	Janssen	Industry trial
Takahashi 2011 (NCT01323192)	OROS methylphenidate	March 2011 – April 2012	Janssen	Industry trial
Spencer 2003 (not registered)	Dex-methylphenidate	Apr 2003 – Sep 2003	Novartis	Industry trial
Huss 2010 (NCT01259492)	Long-acting methylphenidate	Nov 2010 – Aug 2012	Novartis	Industry trial
Rösler 2004 (NCT00619840)	Extended-release methylphenidate	Nov 2004 – May 2006	Medice	Industry trial
Compas 2007 (2006-000222-31)	Extended-release methylphenidate	April 2007 – Aug 2011	German Ministry of Education and Research	Medice was involved in the trial design and data collection
Retz 2008 (NCT00730249)	Extended-release methylphenidate	Sep 2008 – Jan 2010	Medice	Industry trial
Foquest Work 2014 (NCT02225639)	Controlled release methylphenidate	Aug 2014 – May 2015	Purdue	Industry trial
Foquest RCT 2014 (NCT02139124)	Controlled-release methylphenidate	Oct 2014 – Jan 2015	Purdue	Industry trial

[a)] On ClinicalTrials.gov, Massachusetts General Hospital was listed as sponsor and McNeil as collaborator. In the published reports (Biederman et al. 2006 and Biederman et al. 2010), McNeil and Janssen were listed as

sponsors. [b)] On ClinicalTrials.gov, McNeil was listed as collaborator but in the published report McNeil was listed as sponsor (Chronis-Tuscano et al, 2008). [c)] According to ClinicalTrials.gov.

Table 2. Publicly available regulatory documents regarding new drug applications

Regulatory agency	Methylphenidate formulation	Applicant	Regulatory document	Document ID	Regulatory decision
FDA	Dex-MPH ER	Novartis	Drug Approval Package	NDA 21-802	Approved on 26 May 2005
Health Canada	OROS methylphenidate	Janssen	Drug Product Monograph	Submission control no. 224296	Approved on 15 April 2008
FDA	OROS methylphenidate	Janssen	Drug Approval Package	NDA 21-121/S-017	Approved on 27 June 2008
TGA	OROS methylphenidate	Janssen	Prescribing Information	ARTG 93862-4	Approved on 21 Jan 2009
MHRA	OROS methylphenidate	Janssen	Public Assessment Report	UK/H/0544/004/MR	Rejected on 14 July 2010
BfArM	Extended-release methylphenidate	Medice	Public Assessment Report summary	DE/H/2222/001-003/DC, DE/H/2223/001-005/DC	Approved on 18 July 2011
Australia	Long-acting methylphenidate	Novartis	Prescribing Information	ARTG 82957-9	Approved in 2014
MEB	Long-acting methylphenidate	Novartis	Public Assessment Report	116377, 116379-116382	Rejected on 20 Oct 2016
BfArM[a]	Long-acting methylphenidate	Novartis	Public Assessment Report	PL 00101/0973-0977	Approved in 2017
Health Canada	Controlled-release methylphenidate	Purdue	Drug Product Monograph	Submission control no. 214860	Approved on 14 Dec 2017
FDA	Controlled-release methylphenidate	Purdue	Drug approval Package	NDA 212038	Approved on 27 Feb 2019
Health Canada	Controlled-release methylphenidate	Purdue	Drug Product Monograph	Submission control no. 201555	Approved (unknown date)

Listed in chronological order of regulatory decision. [a)] BfArM approved the drug but MHRA published the public assessment report. See references in the supplement.

Table 3. Included and missing participants in regulatory documents

Drug	Regulatory agency	No. included participants (%)	No. missing participants (%)	Total no. participants at time of decision-making
OROS-MPH	Health Canada	402 (28 %)	1057 (72 %)	1459
OROS-MPH	FDA	631 (44 %)	828 (56 %)	1459
Medikinet	BfArM	521 (55 %)	433 (45 %)	954
OROS-MPH	MHRA	1204 (61 %)	754 (39 %)	1958
OROS-MPH	TGA	910 (63 %)	549 (37 %)	1459
Ritalin-LA	TGA	725 (77 %)	221 (23 %)	946
CR-MPH (Foquest)	Health Canada	375 (86 %)	60 (14 %)	435
CR-MPH (Adhansia)	FDA	434 (100 %)	0	434
Ritalin-LA	BfArM	946 (100 %)	0	946
Ritalin-LA	MEB	946 (100 %)	0	946
Dex-MPH	FDA	221 (100 %)	0	221
CR-MPH (Biphentin)	Health Canada	50 (100 %)	0	50

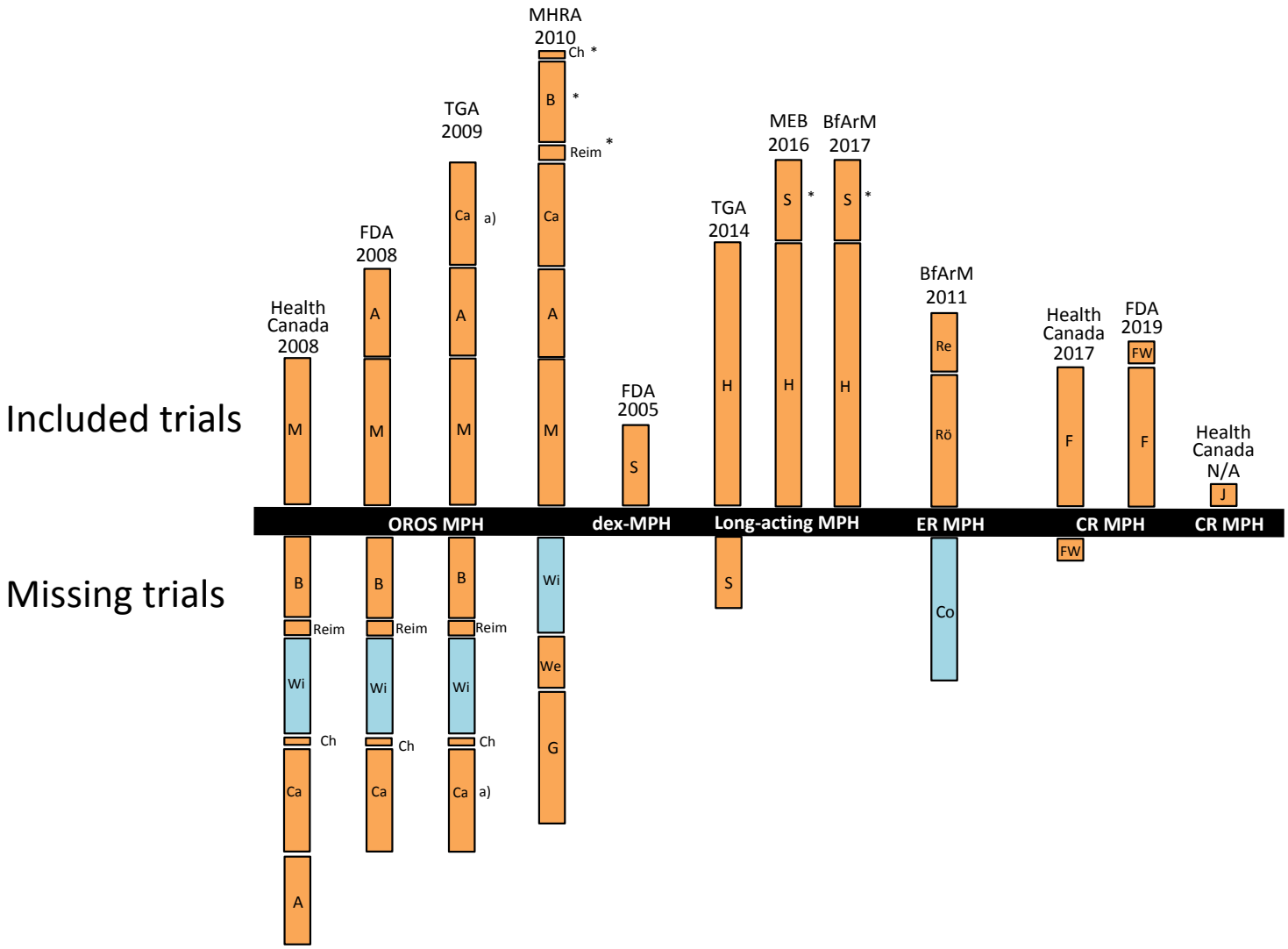
Ongoing trials at time of regulatory decision have been included with their final sample size.

Table 4. Regulatory submission requirements

Regulatory agency	Submission requirements	Where is it described
FDA	"*All controlled clinical studies, including incomplete or abandoned studies, and all pertinent data, whether developed with support of the sponsor or obtained from any other source should be presented in this section" (FDA Guideline)* *"A description and analysis of each controlled clinical study pertinent to a proposed use of the drug, including the protocol and a description of the statistical analyses used to evaluate the study" (eCFR)*	FDA's "Guideline for the Format and Content of the Clinical and Statistical Sections of an Application" The Electronic Code of Federal Regulation, Title 21, part 314
EMA and TGA	"*The purpose of this section is to present a critical analysis of the clinical data pertinent to the efficacy of the medicinal product in the intended population. The analysis should consider all relevant data, whether positive or negative, and should explain why and how the data support the proposed indication and prescribing information" (EMA Guideline)* *"Consequently, an essential requirement is that the results of all clinical trials should be communicated, both favourable and unfavourable" (EU Directive)*	EMA's Guideline on the content of the Common Technical Document EU Directive 2001/83 that specified the content of the Marketing Authorisation Dossier
Health Canada	*" **Attestation:*** *[…]* *2. If applicable:* *a) all pivotal studies included in the submission are complete and final comprehensive analyses provided;* *b) all pivotal data necessary to support the proposed indications, doses and formulations have been provided […]"*	Health Canada's Submission Certificate for a New Drug Submission (NDS)

We focused on EMA's guidelines and the European legislation since the individual European Union members must adhere to these regulations. TGA follows the EMA standards. See eTable 6 and the supplement for references.

Figure 1



Trial abbreviations:

A	Adler (‘06)
B	Biederman (‘03 – ’07)
Ca	Casas (‘08 – ’09)
Ch	Chronis-Tuscano (‘04 – ’05)
CO	COMPAS (‘07 – ’11)
F	Foquest (‘14 – ’15)
FW	Foquest work (’14 – ’15)
G	Goodman (‘09- ’10)
H	Huss (‘10 – ’12)
J	Jain (‘03 – ’04)
M	Medori (‘05 – ’06)
Reim	Reimherr (‘04 – ’05)
Re	Retz (‘08 – ’10)
Rö	Rösler (‘04 – ’06)
S	Spencer (’03)
T	Takahashi (‘11 – ’12)
We	Weisler (’09 - ’10)
Wi	Winhusen (’05 - ’08)

Industry-sponsored trials

Publicly sponsored trials with industry involvement

* Other trial

a) We included the trial on both sides of the bar. The harms, but not the benefits were reported in the document

Scale representing 200 participants

Boesen, Jørgensen, Gøtzsche (2020)

Supplement 1

Appendices

Boesen K, Jørgensen KJ, Gøtzsche PC. How many clinical trials are missing when drug regulators make decisions? A case study of extended-release methylphenidate for adult ADHD.

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eMethods

Cross over trials

In the systematic review, we did not include cross-over trials. For this analysis we included those cross-over trials we identified in our systematic search.

Publicly available resources for regulatory documents

We list the used resources in eTable 1. There are other resources for publicly available documents, most prominently EMA's database of Clinical Study Reports that, until EMA's relocation to Amsterdam, prospectively released clinical study reports (https://clinicaldata.ema.europa.eu/web/cdp/home), and Health Canada's portal that has been prospectively releasing clinical study reports since 2019 (https://clinical-information.canada.ca/search/ci-rc).

Additional drug approvals

The controlled-release methylphenidate formulation marketed by Purdue was approved after we ran our systematic searches of regulatory document databases, as described in our systematic review. We became aware of the approval before this manuscript was finalised and we decided to include it in the cohort of regulatory documents.

eTable 1. Regulatory databases and documents

Regulatory agency	Resource	Type of document	List of submitted trials?	Level of information
FDA	Drugs@FDA	Drug Approval Package (Medical and statistical reviews)	Pivotal studies (yes), other studies (no)	Summary of submitted data on aggregate group level data Summaries of regulatory scientific discussions
EMA	EMA Public Assessment Report database	Public Assessment Report	Pivotal studies (yes), other studies (no)	Summary of submitted data on aggregate group level data Summaries of regulatory scientific discussions
European National Competent Authorities*	National databases of Public Assessment Reports	Public Assessment Report	Pivotal studies (yes), other studies (no)	Summary of submitted data on aggregate group level data Summaries of regulatory scientific discussions
TGA	Australian Public Assessment Report database Australian Register of Therapeutic Goods	Public Assessment Report Prescribing Information and public summary reports	Pivotal studies (yes), other studies (no) Pivotal studies (yes), other studies (no)	Summary of submitted data on aggregate group level data Summaries of regulatory scientific discussions Brief overview of submitted data
Health Canada	Drug Product Database	Drug Product Monographs	Pivotal studies (yes), other studies (no)	Brief overview of submitted data

*For this analysis it entailed MHRA, MEB, and BfArM.

eResults

Index of published and registered extended-release methylphenidate trials

In our systematic search we identified one further publicly funded trial with industry-involvement (https://clinicaltrials.gov/ct2/show/NCT00931398). This trial was never conducted and we decided to not include it in this analysis.

eTable 2. Key trial characteristics of extended-release methylphenidate trials for ADHD in adults

Trial name	Formulation	Trial design	Population	Duration (weeks)	Location	Trial synopsis
BIEDERMAN	OROS-MPH	Parallel group	227	6	United States	Benefits and harms of MPH in adult ADHD
REIMHERR	OROS-MPH	Cross-over	47	4[a]	United States	Benefits and harms of MPH in adult ADHD
CHRONIS-TUSCANO	OROS-MPH	Parallel group	20	2	United States	Benefits and harms of MPH in mother-daughter ADHD dyads
MEDORI	OROS-MPH	Parallel group	402	5	Europe	Benefits and harms of MPH in adult ADHD
WINHUSEN	OROS-MPH	Parallel group	255	11	United States	Benefits and harms of MPH in adult ADHD and smoking cessation
ADLER	OROS-MPH	Parallel group	229	7	United States	Benefits and harms of MPH in adult ADHD
CASAS	OROS-MPH	Parallel group	279	13	Europe	Benefits and harms of MPH in adult ADHD
WEISLER	OROS-MPH	Parallel group	142[b]	6	United States	Benefits and harms of MPH in adult ADHD in comparison with bavisant and atomoxetine
GOODMAN	OROS-MPH	Parallel group	357	6	United States	Benefits and harms of MPH in adult ADHD
TAKAHASHI	OROS-MPH	Parallel group	284	8	Japan	Benefits and harms of MPH in adult ADHD in Japanese population
SPENCER	Dex-ER-MPH	Parallel group	221	5	United States	Benefits and harms of MPH in adult ADHD
HUSS	MPH LA	Parallel group	725	9	Europe, United States, Africa, Asia	Benefits and harms of MPH in adult ADHD
RÖSLER	ER-MPH	Parallel group	359	24	Germany	Benefits and harms of MPH in adult ADHD

RETZ	ER-MPH	Parallel group	162	8	Germany	Benefits and harms of MPH in adult ADHD
COMPAS	ER-MPH	Parallel group	433	52	Germany	Benefits and harms of MPH and group psychotherapy or clinical management in adult ADHD
JAIN	CR-MPH	Cross-over	50	3 - 6 [c]	Canada	Benefits and harms of MPH in adult ADHD
FOQUEST WORK	CR-MPH	Cross-over	60	1[a]	United States	Benefits and harms of MPH in adult ADHD in simulated wok environment
FOQUEST RCT	CR-MPH	Parallel group	375	4	United States and Canada	Benefits and harms of MPH in adult ADHD

OROS = Osmotic Release Oral delivery System, MPH = methylphenidate, CR = controlled-release, ER = extended-release, LA = long-acting. [a)] Duration of the treatment phase before the cross-over. [b)] We counted only the placebo and methylphenidate group sizes, not the bavisant and atomoxetine arms. [c)] Depending on the clinical response, the participants were treated for a shorter or longer period before the cross. See Jain et al. 2007 for details.

eTable 3. Time of registration and publication

Trial name	Formulation	Start - completion	Registered in trial registry (registry link)	First published report (DOI)
BIEDERMAN	OROS-MPH	Jun 2003 – Aug 2007	Sep 2005 (https://clinicaltrials.gov/ct2/show/NCT00181571)	2006 (10.1016/j.biopsych.2005.09.011)
JAIN	CR-MPH	Oct 2003 – April 2004	Not registered	2007 (10.4088/jcp.v68n0213)
REIMHERR	OROS-MPH	Aug 2004 – Dec 2005	Not registered	2007 (10.4088/jcp.v68n0113)
CHRONIS-TUSCANO	OROS-MPH	Dec 2004 – Dec 2006	April 2006 (https://clinicaltrials.gov/ct2/show/NCT00318981)	2008 (10.4088/jcp.v69n1213)
MEDORI	OROS-MPH	Mar 2005 – Nov 2006	Oct 2005 (https://clinicaltrials.gov/ct2/show/NCT00246220)	2008 (10.1016/j.biopsych.2007.11.008)
WINHUSEN	OROS-MPH	Nov 2005 – Mar 2008	Nov 2005 (https://clinicaltrials.gov/ct2/show/NCT00253747)	2010 (10.4088/JCP.09m05089gry)
ADLER	OROS-MPH	Apr 2006 – Dec 2006	May 2006 (https://clinicaltrials.gov/ct2/show/NCT00326391)	2009 (10.1097/JCP.0b013e3181a390ce)
CASAS	OROS-MPH	Feb 2008 – Apr 2009	July 2008 (https://clinicaltrials.gov/ct2/show/NCT00714688)	2013 (10.3109/15622975.2011.600333)
WEISLER	OROS-MPH	May 2009 – Jan 2010	April 2009 (https://clinicaltrials.gov/ct2/show/NCT00880217)	2012 (10.2165/11631990-000000000-00000)
GOODMAN	OROS-MPH	July 2009 – Feb 2010	July 2009 (https://clinicaltrials.gov/ct2/show/NCT00937040)	2016 (10.4088/JCP.15m10348)
TAKAHASHI	OROS-MPH	Mar 2011 - Apr 2012	March 2011 (https://clinicaltrials.gov/ct2/show/NCT01323192)	2014 (10.3109/15622975.2013.868925)
SPENCER	Dex-ER-MPH	Apr 2003 – Sep 2003	Not registered	2007 (10.1016/j.biopsych.2006.07.032)
HUSS	MPH LA	Nov 2010 – Aug 2012	Dec 2010 (https://clinicaltrials.gov/ct2/show/NCT01259492)	2014 (10.1007/s12325-013-0085-5)
RÖSLER	ER-MPH	Nov 2004 – May 2006	Feb 2008 (https://clinicaltrials.gov/ct2/show/NCT00619840)	2009 (10.1007/s00406-009-0005-5)
COMPAS	ER-MPH	April 2007 – Aug 2011[c]	Sep 2006 (https://www.clinicaltrialsregister.eu/ctr-search/trial/2006-	2010 (10.1007/s12402-010-0046-7)

			000222-31/DE)	
RETZ	ER-MPH	Sep 2008 – Jan 2010	Aug 2008 (https://clinicaltrials.gov/ct2/show/NCT00730249)	2012 (10.3109/15622975.2010.540257)
FOQUEST WORK	CR-MPH	Aug 2014 – May 2015	Aug 2014 (https://clinicaltrials.gov/ct2/show/NCT02225639)	Not published
FOQUEST RCT	CR-MPH	Oct 2014 – Jan 2015	May 2014 (https://clinicaltrials.gov/ct2/show/NCT02139124)	Not published

eTable 4. Characteristics of publicly available drug regulatory documents

Regulator	Drug (trade name)	Type of document	Total no. pages	Approx. no. pages with clinical data	Included sections
FDA	Dex-methylphenidate (Focalin XR)	Drug Approval Package[1]	88	40	Integrated review of efficacy; integrated review of safety; statistical evaluation
FDA	OROS methylphenidate (Concerta)	Drug Approval Package[2]	456	58	Integrated review of efficacy; integrated review of safety; statistical evaluation
TGA	OROS methylphenidate (Concerta)	Prescribing Information[3]	20	2	Clinical trials (adults); Adverse effects (adult population)
MHRA	OROS methylphenidate (Concerta)	Public Assessment Report[4]	130	33	Clinical Efficacy (starts p. 34);
Health Canada	OROS methylphenidate (Concerta)	Drug Product Monograph[5]	46	11	Adverse reactions; Clinical Trials [a]
BfArM	Extended-release methylphenidate (Medikinet Retard)	Public Assessment Report summary [6]	7	1,5	Klinische Wirksamkeit; Klinische Sicherheit[b]
TGA	Long-acting methylphenidate (Ritalin LA)	Prescribing Information[7]	23	4,5	Clinical trials; Adverse effects (until postmarketing experiences) [a]
MEB	Long-acting methylphenidate (Ritalin LA)	Public Assessment Report[8]	38	15	Clinical efficacy IV 4.2 Adults; safety;[a] Discussion; Conclusion
BfArM[c]	Long-acting methylphenidate (Ritalin XL)	Public Assessment Report[9]	83	64	Clinical Aspects
Health Canada	Controlled-release methylphenidate (Foquest)[d]	Drug Product Monograph[10]	40	7	Adverse reaction; Clinical Trials[a]
FDA	Controlled-release methylphenidate[d] (Adhansia)	Drug approval Package[11]	171	61	Summary (Clinical/statistical efficacy);[a] Clinical Review; Statistical Review
Health Canada	Controlled-release methylphenidate (Biphentin)	Drug Product Monograph[12]	37	2	Adverse reactions; clinical trials (data from adults only)

The number of pages may vary between the documents for various reasons. For some of them we had to count pages with data from both children and adults. [a)] Included clinical data from trials with children and adults. [b)]We assessed the German, and not the English version, since it contained trial data. [c)] Published by MHRA. [d)] The same drug but approved under different trade names; Foquest in Canada and Adhansia in United States.

eTable 5. Correspondence with drug regulatory agencies

Drug agency	Enquiry submitted	Final answer	Summary of correspondence
BfArM	12 July 2019	19 Feb 2020	We sent one letter regarding two matters: 1. We asked whether Medice informed BfArM about the COMPAS prior to the original approval of extended-release methylphenidate in 2011. 2. We asked about the general procedures regarding submission requirements. BfArM's response: 1. BfArM informed us that Medice did not include COMPAS data in the original application since the trial ended after the drug was approved. 2. BfArM informed us that Medice included data from the COMPAS trial in a type II variation procedure, DE/H/0690/004-010/II/043/G, which was approved in November 2017. 2. BfArM confirmed that an applicant must submit all available evidence as part of the marketing authorisation application.
FDA	19 Dec 2019	26 Dec 2019	We sent one letter, in which we enquired about two matters. 1. We asked whether Janssen had informed FDA about additional trials than those appearing in the drug review. 2. We asked about the general procedures and submission requirements. FDA response: 1. FDA did not directly address our question but referred to the drug approval package. 2. FDA informed that applicants are required to submit all "pertinent" data and referred to the code of federal regulation where it is stated.
MHRA	14 Dec 2019	10 Feb 2020	We sent one letter, in which we enquired about two matters: 1. MHRA published the Public Assessment Report regarding the approval of long-acting methylphenidate (Ritalin LA), but it appeared from the report that MHRA was not the national competent authority that had approved the drug. It was not stated which agency was responsible for the approval. We therefore enquired who had approved the drug.

			2. We also enquired why the drug was assessed and rejected in 2016 by MEB, but the following year assessed and approved by the unknown drug regulatory agency. See our letter in the appendix. MHRA response: 1. MHRA responded that it was BfArM that had approved the drug. 2. MHRA did not address the latter question.
Health Canada	19 Dec 2019	19 June 2020	We sent one letter in which we enquired about two matters: 1. We asked about the approval date of OROS methylphenidate and whether Janssen had informed Health Canada about other clinical trials than those appearing in the Drug Product Monograph. 2. We asked about the general submission requirements and whether the Agency consults with other regulators before decision-making. Health Canada's response: 1. OROS methylphenidate was approved 15 April 2008 for use in adult ADHD. Health Canada provided us Module 2.7 from the Clinical Study Report with a complete list of submitted trials. 2. They informed us they take into consideration other agencies decisions and that the applicant is required to submit all available clinical trials with referral to the submission certificate the applicant must attest prior to submitting data to the agency.
Australian Therapeutic Good Administration	14 Dec 2019	18 May 2020	We sent one letter and one follow-up letter regarding two drugs and the Agency's general drug approval procedure: 1. We asked when OROS methylphenidate was approved and whether Janssen had informed TGA about other trials than those appearing from the Prescribing Information. 2. We asked when Ritalin LA was approved and whether Novartis had informed TGA about other trials than those appearing from the Prescribing Information. 3. We asked about the general submission requirements for new drug applications and whether TGA consults with other agencies. TGA's Response:

			1. OROS methylphenidate was approved in January 2009 but they did not address the remainder of the question and referred me to submit a formal FOIA regarding access to the CSRs. 2. The indication for use of Ritalin LA in adults first appeared in the Product Information in 2014. 3. TGA responded that they have work-sharing agreements and that the Agency generally requires and applicant to submit all available clinical trials.

Status on correspondences, 20 May 2020. See letters and responses in Supplement 2.

eTable 6. List of included and missing trials appearing in regulatory documents

Drug	Regulatory agency	Pivotal trial(s)	Other trial(s)	Missing trials
OROS-MPH	FDA	Medori 2005, Adler 2006	CON-CAN-3,[a] four unknown placebo-controlled trials[b]	Biederman 2003, Reimherr 2004, Chronis-Tuscano 2004, Winhusen 2005, Casas 2008
OROS-MPH	TGA	Medori 2005, Adler 2006, CASAS[c]	None	Biederman 2003, Reimherr 2004, Chronis-Tuscano 2004, Winhusen 2005
OROS-MPH	MHRA	Medori 2005, Adler 2006, Casas 2008	Biederman 2003, Reimherr 2004, Chronis-Tuscano 2004	Winhusen 2005, Weisler 2009, Goodman 2009
OROS-MPH	Health Canada[d]	Medori 2005	CON-CAN-4,[e] C-99-018-00[e]	Biederman 2003, Reimherr 2004, Chronis-Tuscano 2004, Winhusen 2005, Adler 2006, Casas 2008
Dex-MPH	FDA	Spencer 2003	None	None found
LA-MPH	MEB	Huss 2010	Spencer 2003 [f]	None found
LA-MPH	BfArM	Huss 2010	Spencer 2003 [f]	None found
LA-MPH	TGA	Huss 2010	None	Spencer 2003 [e]
ER MPH	BfArM	Rösler 2004, Retz 2008	None	Compas 2007
CR-MPH	Health Canada	Foquest RCT 2014	None	Foquest Work 2014
CR-MPH	FDA	Foquest RCT 2014, Foquest Work 2014	None	None found
CR-MPH	Health Canada	Jain 2003	None	None found

Listed according to drug. [a)] This trial was conducted in adults with major depressive disorder. [b)] These trials were not identified or referenced in the document with a trial ID number, publication name or other identifiers. [c)] Only harms' data were included from the CASAS trial, not its efficacy data. [d)] We had Module 2.7 from the Clinical Study Report available. [e)] Uncontrolled, unblinded trial. [f)] The SPENCER trial assessed dex-methylphenidate. See details in supplement.

Case descriptions of drugs and corresponding regulatory documents

To make the case reports easier to read, we use the trial IDs as reported in eTable 1 based on the author names (in capital letters) of the published reports, rather than the trial registry numbers.

OROS-methylphenidate (Concerta)

Janssen is the marketing authorisation holder of osmotic-controlled release oral delivery system (OROS) methylphenidate, trade name Concerta. We included regulatory documents from three approved applications (FDA, TGA, and Health Canada), and one rejected application (MHRA):

eCase 1: FDA approval (2008)

The US Food and Drug Administration (FDA) approved the formulation for use in children and adolescents with ADHD in 2000 and for use in adults in 2008.

The agreed drug development program between Janssen and the FDA (section 2, p. 76 of 456 and again on p. 119 of 456) consisted of two placebo-controlled trials, MEDORI (called 42603ATT3002 or 3002 in review) and ADLER (called 02-159). A third placebo-controlled randomised clinical trial, CON-CAN-3, was listed under "Other clinical trials". This trial assessed OROS methylphenidate for use in adults with major depressive disorder.

Janssen submitted the last amendment on 13 March 2008 and the FDA approved the drug for use in adult ADHD on 27 June 2008 (FDA Approval letter). According to our trial index, three placebo-controlled trials (BIEDERMAN, REIMHERR, and CHRONIS-TUSCANO) were complete and two trials (CASAS and WINHUSEN) were ongoing (table 1). The CASAS trial had begun five months prior to regulatory decision.

Janssen conducted a literature review and identified four placebo-controlled studies (Section 7.1.1.23, page 125 of 456). FDA commented, "The source papers have not been reviewed at the time of this review" and these studies were not cited or described elsewhere in FDA's review. We can therefore not confirm or reject whether some of the five abovementioned trials, where among these.

There was internal disagreement whether to approve the drug. The FDA medical reviewer expressed concerns about the drug's harms and recommended the conduct of a new trial prior to approval, "Consideration should be given to requiring a large, randomized simple safety trial to look at cardiovascular events […] and making it *a condition for approval*" (Executive summary, p. 72 of 456, FDA's italic). The FDA reviewer had concerns about

cerebrovascular events, "The observation in Study 42603ATT3002 (3002) of *an event rate in excess of the background* [2 events/30 years (Concerta) vs. 150/10.000 person years (background)] is of real concern and should with the recent findings of Gould provide an impetus for making such an action a condition for approval" (Executive Summary, p. 72, FDA's italic). The review's Clinical Team Leader, FDA deputy director of the division of Psychiatry products, Mitchell Mathis, did not agree on the drug-relationship with the serious adverse events (p. 57 of 456). As an example Mathis stated, "Depression is a common disorder and is likely unrelated to study drug. Stimulants, including methylphenidate are often used in practice to treat depression, so the relationship to drug here is not clear". Mathis also did not agree on the need to conduct a new trial. He stated that the risks of cerebrovascular events with methylphenidate was known; that observational data would be sufficient to clarify the risks; and that it would have "practical and ethical limitations" to conduct a new trial (p. 58 of 456). The director of Division of Psychiatry Products, Thomas Laughren, did also not agree on the need for a new trial. Laughren argued, "The study proposed by Dr. Mannheim is simply not feasible. It would need to involve hundreds of thousands of patients, would need a placebo arm, and would take years to complete. In the meantime, the labels for Concerta and other drugs in this class already have very strong warning language that alerts prescribers to possible cardiovascular risks. Thus, I do not agree with the need for the study proposed by Dr. Mannheim, and I will not suggest it to the sponsor" (p. 43 of 456). Laughren approved the drug without further requests to Janssen. We do not know if Janssen was made aware of this internal disagreement and raised criticism by the medical reviewer and if the company were given the chance to supply FDA with the sought-after data. It also seems strange that the need for a new trial is discussed, and discarded, while FDA at the same time overlooked the four (unknown) placebo-controlled trials that Janssen informed them about.

eCase 2: TGA approval (2009)

The Australian Therapeutic Goods Administration approved OROS-MPH for use in adults in January 2009. According to the Product Information (p. 15), the agency approved the drug based on the MEDORI (called study 4) and ADLER (called study 5) trials. Additional harms' data were included from the CASAS trial in a summary table of adverse events (table 3, p. 10). The CASAS trial was not directly cited, but we were able to identify the trial since the MHRA Public Assessment Report included an almost identical adverse event table in their report (MHRA PAR, p. 60). According to the CASAS trial's trial registry entry, the trial was complete a few months after the Australian agency approved the drug. According to our index, four trials were missing, BIEDERMAN, REIMHERR, CHRONIS-TUSCANO, and WINHUSEN (table 1).

eCase 3: MHRA rejection (2010)

The MHRA granted Janssen marketing authorisation for OROS methylphenidate for use in children and adolescents in May 2008 (MHRA PAR, p. 10 of 130). In July 2010, the use in adults was not authorised (MHRA PAR, p. 18 of 130), due to "major efficacy and safety concerns" (MHRA PAR, p. 104 of 130).

According to the MHRA PAR summary (p. 34) three clinical trials in adults were submitted: MEDORI (called 3002), ADLER (called 02-159) and CASAS (called 3013). Additionally, three "non-sponsor initiated trials" were listed, BIEDERMAN, CHRONIS-TUSCANO, and REIMHERR (MHRA PAR, p. 50). These trials were not discussed elsewhere in the review. These trials were listed as "non-sponsor initiated trials", although they listed McNeil as the sponsor in the published reports. McNeil and Janssen both belong to the Johnson & Johnson cooperation. Three OROS methylphenidate trials, WINHUSEN, GOODMAN, and WEISLER, were missing from the MHRA Public Assessment Report. We noted that two clinical trials, not conducted with OROS methylphenidate were mentioned (MHRA PAR, p. 53); RÖSLER, which assessed another extended-release methylphenidate formulation (see below) and then an immediate-release trial we were not able to identify.

The MHRA's statistical assessor raised several methodological concerns, including strict inclusion criteria and the subsequently low prevalence of psychiatric comorbidity in the trial population (p. 36), large dropout rates (p. 39), psychiatric and cardiovascular harms (p. 64), and the lack of long-term data (p. 80).

MHRA concluded, "The totality of the data is therefore weak, with one successful, one borderline failure and one clearly failed trial" (p. 106), referring to the MEDORI, ADLER, and CASAS trials, respectively. The "clearly failed trial", CASAS, did not appear in the FDA Drug Approval Package; in the TGA Prescribing Information only the trial's harms data were included, we do not know when Health Canada approved the drug and therefore whether the drug was missing from the Product Drug Monograph.

eCase 4: Health Canada approval (year unknown)

According to the Drug Product Monograph (table 2.1, p. 31), Health Canada approved OROS methylphenidate for use in adult ADHD based on the MEDORI trial. We have contacted Health Canada regarding the drug approval date since it did not appear from the Monograph, but they have not responded to our enquiry (see eTable 4). Our best estimation of the number of missing trials was therefore to use the MEDORI trial's completion date (November 2006), as a cut-off. Five trials were finished or ongoing by November 2006, BIEDERMAN, REIMHERR, CHRONIS-TUSCANO, WINHUSEN, ADLER. Depending on the time of Health Canada's approval, up to four additional trials may have been missing, CASAS, WEISLER, GOODMAN, and TAKAHASHI.

Extended-release methylphenidate (Medikinet)

eCase 5: BfArM approval (2011)

The German pharmaceutical company Medice is the marketing authorisation holder of the extended-release formulation, trade name Medikinet. It was the first methylphenidate formulation to obtain regulatory approval for use in adults with ADHD in the European Union. The German drug regulator, Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) approved the formulation for use in adults in April 2011.

According to BfArM's Public Assessment Report summary (German Public Assessment Report, section II.4, p. 5), the drug was approved based on two Medice-sponsored trials, RÖSLER and RETZ. In the English Public Assessment Report summary (p. 8), they state that the "majority of the bibliographic data are presented in Module 2.5", which refers to the Clinical Study Report. This indicates that more trials and evidence were presented in the Marketing Authorisation Dossier than is disclosed in the publicly available summary.

We identified a further trial with extended-release methylphenidate in adults, the COMPAS trial, which was ongoing at the time of regulatory decision. This was a publicly funded trial conducted in a time period overlapping with the two pivotal Medice trials, i.e. before the German regulators approved the drug. Although the COMPAS study was funded by two grants from the German Ministry of Education and Research, Medice was involved in the trial. Medice's medical director, Roland Fischer, was acknowledged in several published reports for assisting in designing the protocol and also in collecting the adverse event data.[13-16] Furthermore, a total of four trial authors participated in all three trials involving Medikinet, including the corresponding authors of the three trials' published reports.[15, 17, 18]

Based on BfArM's response to our letter regarding the drug's approval (see eTable 5), Medice did not include data from COMPAS in the original application in 2011. However, Medice did include data from COMPAS in their type II variation, DE/H/0690/004-010/II/043/G. This variation was an expansion of the original indication to also include treatment of adults that have not been treated with methylphenidate in childhood. According to an overview of procedural steps,[19] this particular variation was approved in November 2017. According to the minutes from the European Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) meeting in November 2017,[20] a member state (which one is not reported) had raised concerns regarding PSRPH, Potential Serious Risk for Public Health, related to the variation submission. A PSRPH is raised when there is concern regarding efficacy, safety, quality, a negative risk-benefit assessment, or misleading product information.[21] The PSRPH was raised, "on efficacy and safety, as maintenance of efficacy and cardiovascular and psychiatric safety in long-term in adults were questioned" (CMDh minutes, p. 14 of 24).[20] It was not clear from the CMDh

minutes how the disagreements between the member states were resolved. According to the minutes from the Pharmacovigilance Risk Assessment Committee (PRAC) in July 2018,[22] the member states agreed that a post-authorisation safety study (PASS) should be conducted to assess the long-term cardiovascular and psychiatric harms. The scheduled due date to report results from this study is April 2025, i.e. 14 years after the drug was originally approved by the German regulators.

Dex-methylphenidate (Focalin XL)

Novartis is the marketing authorization holder of dex-methylphenidate, trade name Focalin XL. It was the first extended-release methylphenidate formulation to be approved for use in adult ADHD.

eCase 6: FDA approval (2005)

FDA approved the drug for use in adults in 2005 based on one pivotal trial. According to the FDA Medical Office Review (section 2.5, p. 9), it was agreed between FDA and Novartis on a pre-submission meeting in 2003 that it would be sufficient to submit one randomised trial. From the overview of included trials in FDA's review (section 4.2, p. 10), the SPENCER trial (called 2302) is listed as the only trial conducted in the adult population.

We did not identify other clinical trials conducted with this formulation. We note that the SPENCER trial was included in subsequent drug applications for the other Novartis formulation, long-acting methylphenidate.

Long-acting methylphenidate (Ritalin LA/XL)

Novartis is the marketing authorisation holder of long-acting methylphenidate, trade name Ritalin LA. We included regulatory documents from two approved applications (BfArM and TGA) and one rejected application (MEB). This formulation uses the same extended-release system to release methylphenidate, the Speroidal Oral Drug Absorption System (SODAS), as the dex-methylphenidate formulation. Long-acting methylphenidate contains both stereoisomers, whereas dex-methylphenidate (as the name implies) contains only the right-turned isomer.

eCase 7: MEB rejection (2016)

MEB assessed the drug in 2016 and did not authorise the drug for use in adult with ADHD. In MEB's Public Assessment Report (section 4.2.1, table 8, p. 23), the HUSS trial was listed as the only pivotal trial for the indication in adults.

Similarly to MHRA's assessment of OROS methylphenidate, the MEB report raised several concerns regarding restriction of participants with psychiatric comorbidities (p. 31) and psychiatric adverse events (p. 37). MEB's overall assessment (p. 37) was, "*The evidence presented indicated that the effect size is moderate for this product (ranging between 0.5 and 0.6). The MEB concluded that this does not outweigh the risk of psychiatric adverse events and long-term cardiovascular adverse events and therefore decided that the start of treatment with Ritalin LA in adults is not appropriate"*. They further stated, *"However, the Board acknowledges that it may be appropriate to continue treatment into adulthood in adolescents whose symptoms persist and who have shown clear benefit from treatment."*

The SPENCER trial was mentioned once in the MEB Public Assessment Report. This trial was conducted with Novartis' other extended-release formulation, dex-methylphenidate. It is described in the MEB PAR that Novartis selected the doses used in the HUSS trial based on the SPENCER trial (MEB PAR, p. 23 of 38). MEB compared the HUSS and SPENCER trials' dropout rates caused by psychiatric adverse events (MEB PAR, p. 30): "*Discontinuations due to (any) psychiatric AE occurred in 6.7% of patients included in the controlled Focalin XR-study, but discontinuations due to (any) psychiatric AE in the adult Ritalin LA studies were not specified".* We included SPENCER as an *other* trial, although it was not listed as supportive evidence and it was unclear to what degree the trial was used to inform MEB's decision.

eCase 8: BfArM approval (2017)

BfArM approved the drug in Europe, but for unknown reasons the Public Assessment Report describing the approval process was published by MHRA.

Novartis submitted the HUSS trial and "additional supporting data […] from previous Focalin XR studies in the treatment of adults with ADHD" to support the application (MHRA PAR, section 4.2, p. 41). It was further stated, "*The main focus of this submission is based on the efficacy and safety results from the Phase-III pivotal Study D2302*" (p. 41), with referral to the HUSS trial. We note that the HUSS trial was also the only pivotal trial in the application that MEB rejected in 2016. On page 70, we were able to identify "additional supportive evidence", through the provided trial, ID E2302. We cross-referenced this ID to belong to the SPENCER trial, the dex-methylphenidate trial previously described. The SPENCER trial was not described or discussed in the public assessment report, and its contribution to the overall assessment is unknown.

We noted there were great differences between the MEB and MHRA reports. E.g. the MHRA report did not share MEB's concerns regarding the adverse events, "*The adverse event (A)E profile for the Ritalin LA adult population with ADHD was as expected and was consistent*

with the known AE profile as described in previous reports from paediatric patients with ADHD treated with Ritalin LA" (MHRA PAR, p. 61).

The report concluded, "*Ritalin LA was found to be effective and safe in the short- and long-term treatment of ADHD in adults, in a dose range including 40 mg-80 mg daily. Only few unlabeled adverse events were observed. The adverse effect profile of Ritalin LA in the treatment of adults with ADHD during short and long-term treatment seemed to be similar to that previously observed in the treatment of children with ADHD*" (MHRA PAR, p. 71). Despite relying on the same evidence, the MEB and MHRA reports reflected very different interpretations of the presented benefits and harms. We also note that the MHRA report highlighted SPENCER as supporting evidence, although it was unclear how it contributed to the overall assessment.

eCase 9: TGA approval (2014)

According to correspondence with the Australian Therapeutic Goods Administration, the drug was approved for use in adults in 2014. According to the Prescribing Information (p.5), the drug was approved based on the HUSS trial. Compared to the MEB and MHRA public assessment reports, the SPENCER trial was missing from the Prescribing Information.

Controlled-release methylphenidate (Foquest/Adhansia)

Purdue is the marketing authorisation holder of controlled-release methylphenidate. Health Canada approved the drug for use in adults in 2017 as Foquest and FDA approved the drug in 2019 under the trade name Adhansia. The formulation uses a multilayer release mechanism to ensure a biphasic release of the drug. The ratio between immediate and extended-release methylphenidate is 40/ 60.

eCase 10: Health Canada approval (2017)

According to Foquest's Drug Product Monograph (table 8, p. 29), the approval was based on one clinical trial, FOQUEST RCT (called 063-010).

We identified one other eligible clinical trial, FOQUEST WORK. This trial was described as a "*randomized, double-blind, crossover, placebo-controlled, optimized-dose, phase 3 study to evaluate the safety and efficacy of PRC-063*" in the trial registry entry. First, all participants received methylphenidate during 2 to 7 weeks in an unblinded and uncontrolled "dose-optimisation" phase. Afterwards, the participants were randomised to 1-week active drug or 1-week placebo in a cross-over design. At the end of each treatment period, the participants were tested in an "adult work environment setting" with various tasks and math tests. According to the trial registry entry secondary outcomes included self and investigator rated

ADHD symptoms. The trial matched our inclusion criteria and we included it as a missing trial.

eCase 11: FDA approval (2019)

In contrast to Health Canada, FDA approved the drug based on both the FOQUEST RCT (called 063-010) and the FOQUEST WORK (063-008) trial (FDA Summary, table 1, p. 9). We did not identify missing trials for this drug approval.

The statistical reviewer pointed out that the applicant changed the statistical analysis plan twice after initial agreement with FDA; the statistical model was changed from a mixed method repeated measure to ANCOVA on observed cases, and the primary comparison was changed from the four doses against placebo separately to a pooled estimate of all four doses combined against placebo (FDA Stat, p. 5 bottom). FDA re-ran the analyses with the originally planned methods but there were no important differences between the different methods (FDA Stat Rev, p. 13, table 9 and 10).

Of the three approved doses for use in adults, 25, 45 mg and 70 mg, only the 45 mg dose was statistically significantly better than placebo measured on the primary outcome, the investigator rated symptom scale, ADHD DSM-V in the FOQUEST RCT trial (FDA Stat Rev, p. 13). The 100 mg group was also statistically significantly better than placebo, but the agency judged there was a "disproportionate" increase of harms and did not approve this dose (FDA Clin Rev, p. 8).

Controlled-release methylphenidate (Biphentin)

eCase 12: Health Canada approval (year unknown)

Biphentin is another extended-release methylphenidate formulation marketed by Purdue. It uses the same multilayer release mechanism as Foquest, the only difference between the two drugs being the ratio between immediate and extended-release methylphenidate, which is 20/80 for Biphentin. It is not described in the Drug Product Monograph when the drug was approved.

The Drug Product Monograph lists one clinical trial, JAIN (called study 3 and 022-008), in table 6 (page 30 of 37) and the trial's adverse events are reported in table 3 (page 18 of 37).

We did not identify other clinical trials with this particular formulation. However, JAIN was not registered in a clinical trial registry and we consider it plausible that other clinical trials have been conducted.

When the drug was approved (under the trade name Aptensio) for use in children and adolescents with ADHD by the FDA, we noted that the JAIN trial was included in the New Drug Application (NDA 0205831),[11] see table 3 (page 13 of 63). We further noted that three lines were redacted in the first section of the FDA review, "recommendation on regulatory action", and we can only speculate whether the company also sought approval for use in adults but did not obtain this, since the application included the trial conducted in adults.

Biphentin and Foquest are almost identical drugs; they use the same methylphenidate formulation and the release mechanism is the same. The only difference is the ratio between immediate and extended-release methylphenidate. Whether this is a potential case of evergreening,[12] i.e. an extension of the original patent based on a new marketing authorisation of almost the same drug, is unknown, as we do not know if the patent was extended. We have therefore not included JAIN as a missing trial in the Foquest and Adhansia applications. In the long-acting methylphenidate cases we included the SPENCER trial as missing although it is also not the exactly same drug although the release mechanism and ratio between immediate and extended-release were identical. In these cases, we noted that SPENCER appeared in some documents and not in others, which is why we decided to consider it missing.

eTable 7. Drug regulatory agency submission requirements

Regulator	Regulatory guidelines describing the submission requirements	Legislations or other legal documents describing the requirements
FDA	CDER, "Guideline for the Format and Content of the Clinical and Statistical Sections of an Application" (FDA 1988):[25] Section D, 1, c Submission of all data *"All controlled clinical studies, including incomplete or abandoned studies, and all pertinent data, whether developed with support of the sponsor or obtained from any other source should be presented in this section. For any study intended to support effectiveness the discussion of each study should include the full report described in Section III, but in others an abbreviated report omitting some of the details of study design and effectiveness analyses will be sufficient [See 11.D.2.c.5)].* *The regulation is perhaps ambiguous on where to present a controlled trial available to the sponsor only as a report in the literature, i.e., in the section on controlled trials or in the "other information" section, but it seems best to include all controlled trials pertinent to the claimed effects of the drug in the controlled trials section. Although the absence of case records, an original protocol, and other information would ordinarily limit reliance on these studies, they should be considered as part of the available controlled data base"* (Page 15)	Electronic Code of Federal Regulation, title 21, §314.50:[16] *Section 5* *Clinical data section. A section describing the clinical investigations of the drug, including the following:* *[…]* *"(ii) A description and analysis of each controlled clinical study pertinent to a proposed use of the drug, including the protocol and a description of the statistical analyses used to evaluate the study. If the study report is an interim analysis, this is to be noted and a projected completion date provided. Controlled clinical studies that have not been analyzed in detail for any reason (e.g., because they have been discontinued or are incomplete) are to be included in this section, including a copy of the protocol and a brief description of the results and status of the study."* *[…]* *"(iv) A description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from clinical investigations, including controlled and uncontrolled studies of uses of the drug other than those proposed in the NDA, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers."*
EMA	ICH Topic M 4 E, "Common Technical Document for the Registration of Pharmaceuticals for Human Use – Efficacy"[27] Section 2.5.4 Overview of efficacy *"The purpose of this section is to present a critical analysis of the clinical data pertinent*	EU Directive 2001/83/EC[28] 5.2 Content: Basic principles and requirements *"Special attention shall be paid to the following selected elements. a) The clinical particulars to be provided pursuant to Articles 8 (3) (i) and 10 (1) must enable a sufficiently well-founded and scientifically valid opinion to be formed as to whether the medicinal product satisfies the*

	to the efficacy of the medicinal product in the intended population. The analysis should consider all relevant data, whether positive or negative, and should explain why and how the data support the proposed indication and prescribing information. Those studies deemed relevant for evaluation of efficacy should be identified, and reasons that any apparently adequate and well-controlled studies are not considered relevant should be provided. Prematurely terminated studies should be noted and their impact considered […]"	*criteria governing the granting of a marketing authorisation. Consequently, an essential requirement is that the results of all clinical trials should be communicated, both favourable and unfavourable […]".* (Page 146) *"i) Total or partial omission of data must be explained. Should unexpected results occur during the course of the trials, further pre clinical toxicological and pharmacological tests must be undertaken and reviewed."* (Page 148)
Health Canada	Health Canada informed us that applicants must attest a submission certificate[29] that specifies the following: *"**Attestation:*** *1. All the information and material included in the submission and additional information or material filed to amend the submission are accurate and complete, and the sectional reports and the comprehensive summaries correctly represent the information and material referred to or included in the submission. No information is false or misleading; no omissions have been made that may affect its accuracy and completeness.* *2. If applicable:* *a) all pivotal studies included in the submission are complete and final comprehensive analyses provided;* *b) all pivotal data necessary to support the proposed indications, doses and formulations have been provided;* *c) the formulation used in the studies (clinical and pharmacokinetic) is identical to that proposed for marketing, or evidence that the preparations used in the pivotal clinical efficacy and pharmacokinetic studies are bioequivalent to the preparation to be marketed has been provided. The batch of the drug substance or the final formulation*	We searched the Canadian Food and Drug Act[31] but did not find relevant sections.

	used in pre-clinical studies (especially the carcinogenicity studies) is representative of that proposed for marketing, or acceptable evidence and rationale are provided to defend that any variation does not affect the interpretation of data generated in support of both safety and efficacy." Furthermore, Health Canada uses the Common Technical Document standard,[30] and it seems logical that similar rules apply for Health Canada as for EMA and TGA.	
Australian TGA	TGA have adopted EMA's standard for the Common Technical Document, and TGA specifically refers to the same ICH guideline on the "Clinical overview and clinical summary of module 2" and Module 5: cClinical Study Reports",[32] as used by the EMA. An overview of TGA's submission requirements are available,[33] and an overview of the international guidelines adopted in Australia, including those from EMA, are available.[34]	We searched the Therapeutic Goods Act 1989[35] but did not find relevant sections.

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Supplement 2

Regulatory correspondence

Boesen K, Jørgensen KJ, Gøtzsche PC. How many clinical trials are missing when drug regulators make decisions? A case study of extended-release methylphenidate for adult ADHD.

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Authors' note

We have included only the most relevant letters and emails, e.g. courtesy emails have not been included. However, we have tried to maintain the flow of the correspondences and to avoid that important information was not included.

Regarding the BfArM correspondence

We had previously (letter not included here) submitted a Freedom of Information Act (FOIA) request to access clinical trial data related to the approval of extended-release methylphenidate, trade name Medikinet, marketed by Medice. We were not granted access to the trial data. We followed-up by sending an email regarding the drug approval and the general approval procedures, which is the letter we include here.

Note that we received the final response to our letter on 19 Feb 2020, although BfArM's letter was dated 28 August 2019. We have included BfArM's email to document this delay.

Regarding the Health Canada correspondence

We sent our original letter (included) to the Therapeutic Products Directive, general enquiries (recipient hc.tpdgeneral-generaldpt.sc@canada.ca). On 3 February 2020, we sent a follow-up email to the office of clinical trials (hc.oct.enquiries-requetes.bec.sc@canada.ca).

On 3 April 2020, we submitted a formal FOIA request through the website formula regarding OROS methylphenidate. In Health Canada's response, they attached Module 2.7 from the Clinical Study Report. We have included the document.

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19 December 2019

US Food and Drug Administration
Center for Drug Evaulation and Research (CDER)

We are currently working on a Cochrane systematic review regarding extended-release methylphenidate for adults with attention deficit hyperactivity disorder (ADHD). The protocol for our review is available at the Cochrane Library (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012857/full).

We write to you regarding an extended-release methylphenidate formulation, trade name Concerta. We also have a question about your Agency's general drug approval procedures. If our questions necessitate that we file a Freedom of Information Act request, please consider this letter as such a request.

RE: Osmotic-controlled release oral delivery system (OROS) methylphenidate, trade name Concerta

Janssen is the marketing authorisation holder of Concerta. According to Concerta's FDA Medical Office Review, NDA 21-121/S017, (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/021121s017.pdf) the drug was approved 27 June 2008 for use in adults with attention deficit hyperactivity disorder (ADHD) based on two pivotal clinical trials, NCT00246220 and NCT00326391.

Question regarding your Agency's approval of Concerta

1. Did Janssen inform your Agency about other trials of Concerta for the use in adult ADHD as part of their marketing authorisation application? If this was the case, which trials were they and why were these trials not included in your assessment?

   We are aware of two further trials, NCT00181571 and NCT00714688, which would have been relevant to consider in your assessment, see table 1. The former trial was complete at the time of approval and the latter was ongoing. We note this with interest since the FDA clinical reviewer expressed reservations towards approving Concerta and recommended the conduct of an additional trial as a condition for drug approval: "Consideration should be given to requiring a large, randomized *simple safety trial* to

look at cardiovascular events (e.g. stroke, myocardial infarction and sudden death) and making it *a condition for approval*" (FDA Medical Office Review, page 72 of 456, FDA's italics).

Question regarding your Agency's general drug approval procedures

We also have a question regarding FDA's Manual of Policy and Procedures "Good Review Practice: Clinical Review Template".

In section 5, page A-12, it is stated: "*Potential sources of data for the review include sources within the marketing application (such as submitted final reports) and sources external to the NDA. Consider sources such as these if they have not been included in the NDA/BLA application already: clinical trials conducted by the applicant or designee for similar drugs or for different indications of the same drug, clinical trials conducted by a third party such as the National Institutes of Health, literature reports, and foreign postmarketing safety data collected by foreign regulatory agencies*".

2. Can you please clarify whether the FDA requires an applicant to submit information about *all* available clinical trials related to the specific drug and indication, irrespective of status, sponsor, and outcome, as part of the marketing authorisation application?

Please contact me if my questions need further clarification.

Thank you for your help.

Sincerely,

Kim Boesen, MD
Nordic Cochrane Centre
Rigshospitalet, Dept. 7811
Blegdamsvej 9
2200 Copenhagen Ø
Denmark

Table 1. OROS-methylphenidate (Concerta) trials

Trial ID	Study start – completion	NCT entry	Published report
NCT00181571	June 2003 - Aug 2007	https://clinicaltrials.gov/ct2/show/NCT00181571	Biederman et al, 2010 (doi: 10.1097/JCP.0b013e3181ee84a7)
NCT00246220	Mar 2005 – Nov 2006	https://clinicaltrials.gov/ct2/show/NCT00246220	Medori et al, 2008 (doi: 10.1016/j.biopsych.2007.11.008)
NCT00326391	Apr 2006 – Dec 2006	https://clinicaltrials.gov/ct2/show/NCT00326391	Adler et al, 2009 (doi: 10.1097/JCP.0b013e3181a390ce)
NCT00714688	Feb 2008 - Apr 2009	https://clinicaltrials.gov/ct2/show/NCT00714688	Casas et al, 2013 (doi: 10.3109/15622975.2011.600333)
NCT00937040	July 2009 - Feb 2010	https://clinicaltrials.gov/ct2/show/NCT00937040	Goodman et al, 2016 (doi: 10.4088/JCP.15m10348)
NCT01323192	Mar 2011 - Apr 2012	https://clinicaltrials.gov/ct2/show/NCT01323192	Takahashi et al, 2014 (doi: 10.3109/15622975.2013.868925)

Legend. Data taken from the clinicaltrials.gov entries. The highlighted trials were included in FDA's Medical Office Review of Concerta.

RE: Questions about drug approvals

CDER DRUG INFO <DRUGINFO@fda.hhs.gov> Thu, Dec 26, 2019 at 3:37 PM
To: "kb@cochrane.dk" <kb@cochrane.dk>

Dear Dr. Boesen,

Thank you for writing the Division of Drug Information in the FDA's Center for Drug Evaluation and Research.

Information on the clinical trials FDA reviewed for the approval of Concerta is available on Drugs@FDA in the review package noted in your email. The approval letter did not state that additional studies were required to be conducted post-approval.

NDA's are required to contain reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent to an evaluation of the NDA that is received or otherwise obtained by the applicant from any source. For more information, please review 21 CFR 314.50 and Resources for NDA Submissions.

Visit How to Make a FOIA Request for instructions about how to submit via mail or online. Fees may be required to process your request. For more information about applicable fees, please visit FOIA Fees. For more information about FOIA, visit: Frequently Asked Questions for Freedom of Information. Before submitting a FOIA request, please check to ensure the records are not already available online in an Electronic Reading Room.

Best regards,

SB

Drug Information Specialist

Division of Drug Information

Center for Drug Evaluation and Research

Tel: 855-543-DRUG (855-543-3784)

druginfo@fda.hhs.gov

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This communication is consistent with 21 CFR 10.85(k) and constitutes an informal communication that represents our best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

From: Kim Boesen <kb@cochrane.dk>
Sent: Thursday, December 19, 2019 6:05 PM
To: CDER DRUG INFO <DRUGINFO@fda.hhs.gov>
Subject: Questions about drug approvals

To whom it may concern,

Please see the attached letter.

Kindly acknowledge upon receipt.

Sincerely,

Kim Boesen
--

Kim Boesen, MD

Researcher

Nordic Cochrane Centre

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14 December 2019

Medicines and Healthcare products Regulatory Agency
London
United Kingdom

We are currently working on a Cochrane systematic review regarding extended-release methylphenidate for adults with attention deficit hyperactivity disorder (ADHD). The protocol for our review is available at the Cochrane Library (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012857/full).

We write to you regarding an extended-release methylphenidate formulation, trade name Ritalin XL/LA:

According to MHRA's Public Assessment Report of Ritalin XL/LA, reference PL 00101/0973-0977, (http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con870423.pdf), the MHRA participated in an "informal work sharing procedure" (p. 41) together with (we assume) the country that approved the drug for use in adult ADHD in the EU. The drug was granted UK marketing authorisation for use in adults with ADHD on 20 December 2017.

We have two questions regarding the drug approval of Ritalin XL. If our questions necessitate that we file a formal Freedom of Information Act request, please consider this letter such a request.

1. Can you please clarify to us which national competent authority was responsible for approving Ritalin XL/LA for use in adult ADHD? We have not been able to identify the relevant authority through the reference ID (DE/H/XXXX/WS/056) listed in your Public Assessment Report (p. 41). We have also not been able to locate the reference member state through the Heads of Medicines' MRI Product Index. We assume that Germany is the reference member state, based on the ID prefix, but we would appreciate if you could provide this information.

2. We note that the Dutch Medicines Evaluation Board (MEB) assessed the Ritalin XL formulation for regulatory approval already in 2016 (NL License RVG: 116377, 116379-116382). According to the MEB Public Assessment Report (https://db.cbg-meb.nl/Pars/h116381.pdf), the MEB approved the drug for use in children and adolescents with ADHD, but they did not grant authorisation for use in adults (p. 3). Since

your Agency seems to have been involved in the approval of the drug the following year, can you help clarify the chronology of the Ritalin XL approval procedure and clarify the rationale for having two different European national competent authorities assessing the same drug, for the same indication, within a year?

Please do not hesitate to contact me if our questions need further clarification.

Thank you for your help.

Sincerely,

Kim Boesen, MD
Nordic Cochrane Centre
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151 Buckingham Palace Road
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London SW1W 9SZ
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Email
FOILicensing@mhra.gsi.gov.uk
mhra.gov.uk

10 February 2020

Dear Dr Kim Boese,

Ref: GCEP-00141556– Question regarding Ritalin XL approval

Thank you for your letter dated 14 December 2019, where you asked the following questions regarding an extended-release methylphenidate formulation, trade name Ritalin XL/LA, for the treatment of attention deficit hyperactivity disorder (ADHD). Please find our responses to your questions below.

1. **Can you please clarify to us which national competent authority was responsible for approving Ritalin XL/LA for use in adult ADHD? We have not been able to identify the relevant authority through the reference ID (DE/H/XXXX/WS/056) listed in your Public Assessment Report (p. 41). We have also not been able to locate the reference member state through the Heads of Medicines' MRI Product Index. We assume that Germany is the reference member state, based on the ID prefix, but we would appreciate if you could provide this information.**

   We confirm that Germany was the Reference Member State (RMS) for the specified work-sharing procedure (DE/H/XXXX/WS/056), to extend the already approved indication of ADHD in children and young people (between 6 and 18 years) to adults.

2. **We note that the Dutch Medicines Evaluation Board (MEB) assessed the Ritalin XL formulation for regulatory approval already in 2016 (NL License RVG: 116377, 116379-116382). According to the MEB Public Assessment Report (https://db.cbgmeb.nl/Pars/h116381.pdf), the MEB approved the drug for use in children and adolescents with ADHD, but they did not grant authorisation for use in adults (p. 3). Since your Agency seems to have been involved in the approval of the drug the following year, can you help clarify the chronology of the Ritalin XL approval procedure and clarify the rationale for having two different European national competent authorities assessing the same drug, for the same indication, within a year?**

   The product licences for Ritalin LA 10, 20, 30, 40 & 60 mg modified-release capsules (NL License RVG: 116377, 116379, 116380, 116381 & 116382) were granted by the Netherlands through their own national procedure on 30 August 2016. The product licences for Ritalin XL 10, 20, 30, 40 & 60 mg modified-release hard capsules (PL 00101/0973, 0974, 0975, 0976 & 0977) were granted by the UK through our national procedure on 20 December 2017. In the UK, as Ritalin XL modified-release hard capsules are line extensions of Ritalin 10mg Tablets (PL 00101/0539), which was originally granted through a national procedure in the UK on 30 August 1988, these licences could also be assessed via a national procedure, Regarding the timelines for the UK assessment of Ritalin XL modified-release hard capsules, please see below the chronology for MHRA's assessment of these products:

Application received	29/01/2015
Grant	20/12/2017

We now consider this request closed. If you require any further information, please respond to the FOI Licensing Team at FOILicensing@mhra.gov.uk.

Yours sincerely,

Medical Writer
Licensing Team

Copyright notice

The information supplied in response to your request is the copyright of MHRA and/or a third party or parties, and has been supplied for your personal use only. You may not sell, resell or otherwise use any information provided without prior agreement from the copyright holder.
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14 December 2019

Australian Government
Department of Health
Therapeutics Goods Administration

We are currently working on a Cochrane systematic review regarding extended-release methylphenidate for adults with attention deficit hyperactivity disorder (ADHD). The protocol for our review is available at the Cochrane Library (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012857/full).

We write to you regarding two extended-release methylphenidate formulations, trade names Concerta and Ritalin LA, that your Agency has approved. We also have two questions about your Agency's general drug approval procedures. If our questions necessitate that we file a Freedom of Information Act request, please consider this letter such a request.

RE: Osmotic-controlled release oral delivery system (OROS) methylphenidate, trade name Concerta

Janssen is the marketing authorisation holder of Concerta. According to Concerta's Product Information (ARTG ID: 93864) available from the Australian Register of Traded Goods (https://www.tga.gov.au/artg), the drug was approved for use in adults with ADHD based on two clinical trials referred to as "Study 4" and "Study 5" (Product information, p. 3).
We have identified these trials NCT00246220 and NCT00326391, respectively.

For the safety assessment, your Agency included one further clinical trial conducted in adults with ADHD (Product Information, table 2, p. 9). Based on an almost identical adverse event table in the British Medicines and Healthcare products Regulatory Agency (MHRA) assessment report of the same drug (UK/H/0544/004/MR, p. 60), we have identified the trial as NCT00714688.

Questions regarding your Agency's approval of Concerta

1. Can you specify when (year and date) your Agency approved Concerta for use in adults with ADHD, as this is not stated in the Product Information?

2. What was the reason for including the NCT00714688 trial data only in the safety assessment and not also in the efficacy assessment?

3. Did Janssen inform your Agency about other trials of Concerta for the use in adult ADHD as part of their marketing authorisation application? If this was the case, which trials were they and why were these trials not included in your assessment?

   We are aware of three other clinical trials of Concerta for adults with ADHD that, depending on the time of your approval, would have been relevant to include in the marketing authorisation application, **table** 1.

Questions regarding your Agency's general drug approval procedures

4. Based on the three clinical trials that your Agency used to approve Concerta for use in adults with ADHD, the British drug regulatory authority, MHRA, decided to not approve Concerta for use in adults (Public Assessment Report, http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con2033483.pdf). Does your Agency normally consult with other drug regulatory agencies regarding their decisions, prior to approving or rejecting a marketing authorisation application?

5. Does your Agency require an applicant to submit information from *all* available clinical trials related to the specific drug and indication, irrespective of status, sponsor, and outcome of a trial, as part of the marketing authorisation application?

RE: Ritalin LA

Ritalin LA is an extended-release formulation marketed by Novartis. According to Ritalin LA's Product Information, ARTG ID: 82959 (https://www.tga.gov.au/artg), this drug was approved for use in adults with ADHD based on one clinical trial, which we have identified as NCT01259492 (https://clinicaltrials.gov/ct2/show/NCT01259492).

Questions regarding your Agency's approval of Ritalin LA

1. Can you specify when (year and date) your Agency approved the drug for use in adults, as this is not stated in the product information?

2. Did Novartis submit clinical trial data only from the NCT01259492 trial mentioned in the Product Information, or did they include information from other clinical trials in adults with ADHD in their marketing authorisation application? If this was the case, which were these trials and why were they not listed in the Product Information?

Please do not hesitate to contact me if my questions need further clarification.

Thank you for your help.

Sincerely,

Kim Boesen, MD
Nordic Cochrane Centre
Rigshospitalet, Dept. 7811
Blegdamsvej 9
2200 Copenhagen Ø
Denmark

Table 1. OROS-methylphenidate (Concerta) trials

Trial ID	Study start – completion*	NCT entry	Published report
NCT00181571	June 2003 - Aug 2007	https://clinicaltrials.gov/ct2/show/NCT00181571	Biederman et al, 2010 (doi: 10.1097/JCP.0b013e3181ee84a7)
NCT00246220 (LAMDA-I)	Mar 2005 – Nov 2006	https://clinicaltrials.gov/ct2/show/NCT00246220	Medori et al, 2008 (doi: 10.1016/j.biopsych.2007.11.008)
NCT00326391	Apr 2006 – Dec 2006	https://clinicaltrials.gov/ct2/show/NCT00326391	Adler et al, 2009 (doi: 10.1097/JCP.0b013e3181a390ce)
NCT00714688 (LAMDA-II)	Feb 2008 - Apr 2009	https://clinicaltrials.gov/ct2/show/NCT00714688	Casas et al, 2013 (doi: 10.3109/15622975.2011.600333)
NCT00937040	July 2009 - Feb 2010	https://clinicaltrials.gov/ct2/show/NCT00937040	Goodman et al, 2016 (doi: 10.4088/JCP.15m10348)
NCT01323192	Mar 2011 - Apr 2012	https://clinicaltrials.gov/ct2/show/NCT01323192	Takahashi et al, 2014 (doi: 10.3109/15622975.2013.868925)

Legend. Data taken from the clinicaltrials.gov entries. The highlighted trials are included in the Australian Concerta Product Information.

RE: Drug approval questions [SEC=OFFICIAL]

TGA FOI <TGAFOI@health.gov.au> Thu, Jan 16, 2020 at 2:01 AM
To: "kb@cochrane.dk" <kb@cochrane.dk>
Cc: TGA FOI <TGAFOI@health.gov.au>

Dear Dr Boesen

Thank you for your email, and please accept our sincere apologies for the delay in responding to you.

We have been consulting with relevant areas to determine what information we can provide to you now and what must be requested, due to potential commercial sensitivities, under the *Freedom of Information Act 1982* (the FOI Act).

Information that is publicly available is as follows:

- For an overview of the process and considerations for registering a prescription medicine, please see the TGA website here: www.tga.gov.au/australian-regulation-prescription-medical-products.
- The TGA has international work-sharing arrangements which can be viewed here: www.tga.gov.au/publication/comparable-overseas-regulators-cors-prescription-medicines.
- The TGA generally does require an applicant to submit information from all available clinical trials related to the specific drug and indication, as part of the marketing authorisation application.

Information regarding the date of registration for medicines on the ARTG is available on the TGA's website via the specific ARTG entry:

Concerta was registered on the ARTG on 3 September 2003
https://www.ebs.tga.gov.au/servlet/xmlmillr6?dbid=ebs/PublicHTML/pdfStore.nsf&docid=E4390AA1916B84D9CA258447004213AE&agid=(PrintDetailsPublic)&actionid=1

Ritalin LA was registered on 12 August 2002.

https://www.ebs.tga.gov.au/servlet/xmlmillr6?dbid=ebs/PublicHTML/pdfStore.nsf&docid=3BE373A93DCAB345CA258481004219FC&agid=(PrintDetailsPublic)&actionid=1

Information in regard to clinical trials (other than that which is already publicly available) must be requested under the FOI Act, noting the potential associated commercial sensitivities. Accordingly, we provide the following information:

Submitting an FOI request

Section 15 of the FOI Act requires that a request for access meets certain requirements. Your request, in its current form, does not constitute a valid request as it is a request for information rather than documents. The FOI Act only provides for access to documents and not to 'information'.

In order for your request to be processed under the provisions of the FOI Act we require further information to enable us to identify the **document** or **documents** you are seeking. As such, you may wish to consider submitting the following scope:

> *"For the purposes of the Freedom of Information Act, I seek access to a summary of the clinical trials submitted and evaluated during the application for market authorisation for Concerta and Ritalin LA"*

Please note that this scope is a suggestion only. At this early stage, the TGA is unable to advise whether it may be too voluminous to process or if any documents will be returned.

Alternatively, we would greatly appreciate if you could provide us with more information on the specific documents that you require.

Please note until your request meets the requirements of Section 15 of the FOI Act, we are unable to process your request, and no further action will be taken in relation to this matter.

I hope this is helpful. If you have any questions about the FOI process, please get in touch.

Again, please accept our apologies for the delay.

Kind regards

Kyla

Freedom of Information

Kyla | Karen | Tara | Cindy

Therapeutic Goods Administration

Australian Government Department of Health

T: 02 6289 4630 | E: TGAFOI@health.gov.au

PO Box 100, Woden ACT 2606, Australia

Web: www.tga.gov.au

Important: *This transmission is intended only for the use of the addressee and may contain confidential or legally privileged information. If you are not the intended recipient, you are notified that any use or dissemination of this communication is strictly prohibited. If you receive this transmission in error please notify the author immediately and delete all copies of this transmission.*

The Department of Health acknowledges the Traditional Custodians of Australia and their continued connection to land, sea and community. We pay our respects to all Elders past and present.

From: Kim Boesen <kb@cochrane.dk>
Sent: Sunday, 15 December 2019 11:58 AM
To: Clinical Trials <clinical.trials@tga.gov.au>
Subject: Drug approval questions [SEC=No Protective Marking]

To whom it may concern,

Please see the attached letter.

Kindly acknowledge receipt of this email.

Sincerely,

Kim Boesen

--

Kim Boesen, MD

Researcher

Nordic Cochrane Centre

"Important: This transmission is intended only for the use of the addressee and may contain confidential or legally privileged information. If you are not the intended recipient, you are notified that any use or dissemination of this communication is strictly prohibited. If you receive this transmission in error please notify the author immediately and delete all copies of this transmission."

Boesen_Letter_Australia_141219.pdf
162K

RE: Drug approval questions [SEC=OFFICIAL]

Kim Boesen <kb@cochrane.dk> Tue, Jan 21, 2020 at 1:15 AM
To: TGA FOI <TGAFOI@health.gov.au>

Dear Kyla,

Thank you very much for your kind reply. I have a few clarifying questions:

1. The dates you provided regarding Concerta and Ritalin XL's drug approvals seem to be for the drugs' initial approvals. These approvals were only for use in children and adolescents and the drugs were approved for use in adults much later. For instance, FDA approved Concerta for use in children and adolescents in 2000 and in 2008 for use in adults. If you can help us find out when these two drugs were approved by the TGA for use in adults with ADHD, it would be much appreciated.

2. Regarding what specific documents to request: I have already searched for Concerta and Ritalin XL's Public Assessment Reports in the AusPAR database but it did not return any hits. Does this indicate that the TGA did not make Public Assessment Reports when the drugs were approved, or does it mean that th Public Assessment Reports are not publicly available and I will have to specifically request access to them?

If there are no available Public Assessment Reports, the next step would be to ask for access to specific parts of the submitted marketing authorisation dossiers. Since the TGA has adopted the EMA's definition of "commercially confidential information" (https://www.tga.gov.au/sites/default/files/regulation-basics-disclosure-cci-140514.pdf), I would assume that I could ask for access to Module 5 (clinical study reports), or specific specific parts of it? Considering that TGA follows the Common Technical Document structure (https://www.tga.gov.au/publication/common-technical-document-ctd), that would entail section 5.2 of the clinical study report, i.e. "Tabular listing of all clinical studies".

Sincerely,

Kim Boesen
[Quoted text hidden]

RE: Drug approval questions [SEC=OFFICIAL]

TGA FOI <TGAFOI@health.gov.au> Thu, Jan 23, 2020 at 12:38 AM
To: Kim Boesen <kb@cochrane.dk>
Cc: TGA FOI <TGAFOI@health.gov.au>

Dear Kim

Thank you for your email. We have consulted with the business area to provide responses to your questions below (in red).

We hope these responses are helpful, please get in contact if any clarification is needed.

Thank you

Kyla

Freedom of Information

Kyla | Karen | Tara | Cindy

Therapeutic Goods Administration

Australian Government Department of Health

T: 02 6289 4630 | E: TGAFOI@health.gov.au

PO Box 100, Woden ACT 2606, Australia

Web: www.tga.gov.au

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From: Kim Boesen <kb@cochrane.dk>
Sent: Tuesday, 21 January 2020 11:15 AM
To: TGA FOI <TGAFOI@health.gov.au>
Subject: Re: Drug approval questions [SEC=OFFICIAL]

Dear Kyla,

Thank you very much for your kind reply. I have a few clarifying questions:

1. The dates you provided regarding Concerta and Ritalin XL's drug approvals seem to be for the drugs' initial approvals. These approvals were only for use in children and adolescents and the drugs were approved for use in adults much later. For instance, FDA approved Concerta for use in children and adolescents in 2000 and in 2008 for use in adults. If you can help us find out when these two drugs were approved by the TGA for use in adults with ADHD, it would be much appreciated. January 2009.

2. Regarding what specific documents to request: I have already searched for Concerta and Ritalin XL's Public Assessment Reports in the AusPAR database but it did not return any hits. Does this indicate that the TGA did not make Public Assessment Reports when the drugs were approved, or does it mean that th Public Assessment Reports are not publicly available and I will have to specifically request access to them? These documents do not exist as AusPARs were not published prior to 2009.

If there are no available Public Assessment Reports, the next step would be to ask for access to specific parts of the submitted marketing authorisation dossiers. Since the TGA has adopted the EMA's definition of "commercially confidential information" (https://www.tga.gov.au/sites/default/files/regulation-basics-disclosure-cci-140514.pdf), I would assume that I could ask for access to Module 5 (clinical study reports), or specific specific parts of it? Considering that TGA follows the Common Technical Document structure (https://www.tga.gov.au/publication/common-technical-document-ctd), that would entail section 5.2 of the clinical study report, i.e. "Tabular listing of all clinical studies". The TGA would need to conduct a search and retrieval in order to ascertain whether these documents exist. Therefore, the submission of an FOI request would be appropriate. Alternative documents that may contain this information are ADEC resolutions or the Delegate's Overview (again without doing a search and retrieval we cannot guarantee these documents exist). We not that, without consulting the relevant third party, the TGA cannot provide advice on whether this information may be exempt under the FOI Act.

Sincerely,

Kim Boesen

[Quoted text hidden]

RE: Drug approval questions [SEC=OFFICIAL]

Kim Boesen <kb@cochrane.dk> Thu, Feb 13, 2020 at 4:14 AM
To: TGA FOI <TGAFOI@health.gov.au>

Dear Kyla,

Thank you very much for your thorough answer. I will not need to file a formal Freedom of Information Act request for now, but I have one final answer I hope you can help clarify.

You answered that Concerta was approved for use in adults with ADHD in 2009. Can you also inform us when Ritalin XL (marketed by Novartis) was approved by the TGA for use in adults with ADHD? I know that the drug was approved for this indication in EU in 2017.

Again thank you very much for your help.

Sincerely,
Kim
[Quoted text hidden]

RE: Drug approval questions [SEC=OFFICIAL]

TGA FOI <TGAFOI@health.gov.au> Fri, Feb 28, 2020 at 2:17 AM
To: Kim Boesen <kb@cochrane.dk>
Cc: TGA FOI <TGAFOI@health.gov.au>

Dear Kim

I apologise for the delay in responding to your email.

I am advised that the line area has requested offsite files in order to address your questions and will respond shortly.

We will contact you once we receive their response.

Kind regards
Karen

[Quoted text hidden]
[Quoted text hidden]

RE: Drug approval questions [SEC=OFFICIAL]

TGA FOI <TGAFOI@health.gov.au> Mon, May 18, 2020 at 7:22 AM
To: Kim Boesen <kb@cochrane.dk>
Cc: TGA FOI <TGAFOI@health.gov.au>

Dear Kim

Thank you for your patience. The line area have now provided the following response to your enquiry:

> *By way of background, Ritalin was a grandfathered product that was entered onto the Australian Register Therapeutic Goods for use in ADD (now ADHD). Grandfathered products are those products that were available in Australia prior to the Act coming into effect in 1990. At this time, the approved indications for Ritalin did not expressly state the product was for use in children (only).*
>
> *In 2001 the TGA received an application to register 20mg, 30mg and 40mg modified release capsules (Ritalin LA). The relevant Product Information for this product made reference to use in adults, however the indications did not expressly state any specific age groups for the relevant indications.*
>
> *It is noted that at this time it was common for indications to not include specific age group populations.*
>
> *Adults were first expressly mentioned in the Product Information which was approved on 28.10.2014.*

I hope this answer is helpful.

[Quoted text hidden]
[Quoted text hidden]

Cochrane Nordic

Trusted evidence. Informed decisions. Better health.

Nordic Cochrane Centre
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Blegdamsvej 9
2100 Copenhagen Ø, Denmark
Tel: +45 35 45 71 12
E-mail: general@cochrane.dk
www.nordic.cochrane.org

Copenhagen
12 July 2019

Dear B. Michel-Lukacs,

Thank you for your email and letter of 4 June 2019 with your final decision to reject my freedom of information act request for access to clinical trial data underlying the drug approval of extended-release methylphenidate (tradename Medikinet) for adults with ADHD. I have four follow-up questions I hope you can answer, irrespective of your rejection of my request. The first three questions relate directly to my original request and I hope these can be answered without the need to file a new freedom of information act request. The final question relates to the general procedures of BfArM.

Background information to my questions

According to the extended-release methylphenidate (tradename Medikinet) public assessment report (DE/H/2222/001-003 and DE/H/2223/001-005) from 18 July 2011, the drug approval was based on two clinical trials, both of which were sponsored by the applicant Medice:

1) The EMMA trial (https://clinicaltrials.gov/ct2/show/NCT00619840), which ran from November 2004 to May 2006.

2) The QUMEA trial (https://clinicaltrials.gov/ct2/show/NCT00730249), which ran from September 2008 to January 2010.

During the same period, the German Ministry of Education and Research funded a third clinical trial of extended-release methylphenidate (tradename Medikinet):

3) The COMPAS trial (http://www.isrctn.com/ISRCTN54096201), which ran from November 2006 to August 2011.

The COMPAS trial was funded by two public grants, 01GV0605 and 01GV0606 (https://www.gesundheitsforschung-bmbf.de/de/psychotherapie-2956.php), the first of which was assigned in 2006. Medice provided the study medication and Medice's medical director, Roland Fischer, is acknowledged by the COMPAS trial authors in several published journal

articles for his assistance in preparing the study protocol and case report forms, and assisting in the serious adverse event management.

Three questions related to Medikinet's approval:

1. Did Medice inform BfArM about the COMPAS trial in their marketing authorisation application for Medikinet?
2. If Medice informed BfArM about the COMPAS trial, was clinical trial data from COMPAS included in BfArM's assessment report of Medikinet?
3. If yes, why was this data not mentioned in the public assessment report?

General question about BfArM's procedures:

4. Does BfArM require an applicant to submit information from *all* available clinical trials related to the specific drug and condition, despite status, sponsor, and outcome of a trial, as part of the marketing authorisation application?

Please do not hesitate to contact me if you need further clarification.

Sincerely,

Kim Boesen

Re: GZ 1273-(BfArM) IFG-Anfragen 2019#0027-IFG, Nordic Cochrane Centre, Methylphenidate #0011 Antwort

Michel-Lukacs, Beatrix <Beatrix.Michel-Lukacs@bfarm.de> Wed, Feb 19, 2020 at 4:39 PM
To: Kim Boesen <kb@cochrane.dk>

Dear Ms. Boesen,

thank you for your writing. We regret that you have not received our answer yet. It is from August 2019 and we thought it had reached you then.

Kind regards

B. Michel-Lukacs

Bundesinstitut für Arzneimittel-und Medizinprodukte

Justiziariat

Kurt-Georg-Kiesinger-Allee 3

53175 Bonn

Germany

Phone +49-228-99307-5835

Email: Beatrix.Michel-Lukacs@bfarm.de

Federal Institute for Drugs and Medical Devices

The BfArM is a Federal Institute within the portfolio of the Ministry of Health

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Von: Kim Boesen <kb@cochrane.dk>
Gesendet: Montag, 13. Januar 2020 20:13
An: Michel-Lukacs, Beatrix <Beatrix.Michel-Lukacs@bfarm.de>
Betreff: Re: GZ 1273-(BfArM) IFG-Anfragen 2019#0027-IFG, Nordic Cochrane Centre, Methylphenidate #0011 Antwort

Dear B. Michel-Lukacs,

Referring to our previous correspondence, I would like to know when I can expect a final answer to my Freedom of Information Act request (reference number 2019#0070), which was originally submitted 12 July 2019. I have been informed by my department that the bill for processing the request was received on 18 Oct 2019 and that it was paid on 28 November 2019.

I am looking forward to hearing from you.

Sincerely,

Kim Boesen

On Mon, Aug 12, 2019 at 5:11 AM Kim Boesen <kb@cochrane.dk> wrote:

Dear B. Michel-Lukacs,

Thank you very much for your emails. I would like to maintain my request and accept the conditions you have stated. If you provide me with the details for paying the fee, I will take care of this immediately.

Can you give an estimate of when I can expect to receive a final response?

Thank you very much for your help.

Sincerely,

Kim Boesen

Antwort.docx
48K

Bundesinstitut
für Arzneimittel
und Medizinprodukte

BfArM, Kurt-Georg-Kiesinger-Allee 3, 53175 Bonn

Nordic Cochrane Centre

Mr. Kim Boesen
Blegdamsvej 9
2100 Copenhagen Ø
Denmark

ABTEILUNG Verwaltung/Justiziariat
BEARBEITET VON Beatrix Michel-Lukacs
TEL +49 (0)228 99 307-5835
E-MAIL Beatrix.Michel-Lukacs@bfarm.de

HAUSANSCHRIF Kurt-Georg-Kiesinger-Allee 3
T 53175 Bonn
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FAX +49 (0)228 99 307-5207
E-MAIL poststelle@bfarm.de
INTERNET www.bfarm.de

Bonn, 28. August 2019
GESCHZ Z161.06-2019-29459

NACHFRAGE - Medikenet, clinical trial data

Ihre Zeichen und Nachricht vom: 07.08.2019

Dear Ms. Boesen,

with respect to your three questions related to Medikinet's approval we can answer the following:

1. **Did Medice inform BfArM about the COMPAS trial in their marketing authorisation application for Medikinet?**

Medice included information on the COMPAS trial in Variation Procedure **DE/H/0690/004-010/II/043/G for Medikinet retard.** The scope of this variation was to extend the indication (section 4.1) to the possibility of starting the treatment in adults:

"*Attention-Deficit/Hyperactivity Disorder (ADHD)*
Methylphenidate is indicated as part of a comprehensive treatment program for attention-deficit / hyperactivity disorder (ADHD) in children aged 6 years of age and over, adolescents and adults when remedial measures alone prove insufficient…."

2. **If Medice informed BfArM about the COMPAS trial, was clinical trial data from COMPAS included in BfArM's assessment report of Medikinet?**

Yes, available data of the COMPAS trial was evaluated within procedure **DE/H/0690/004-010/II/043/G** for Medikinet retard and is mentioned in the Final Variation Assessment Report as supportive information. Therefore, the PARs of procedure DE/H/0690 (see attached documents) were updated with the indication extension in accordance with the "CMDh BPG for Public Assessment Report and Summary PAR in MRP/DCP".

3. **If yes, why was this data not mentioned in the public assessment report?**

Please note that the approval of Medikinet adult was in a different procedure. As you might have noticed from the EPAR, the variation procedure of Medikinet adult was in a purely national procedure, which was approved on 14 April 2011 based on results of the QUEMA and EMMA studies. At that time the COMPAS study had still been running (recruitment end 31 October 2011) and results could not be submitted.

General question about BfArM's procedures:

4. **Does BfArM require an applicant to submit information from all available clinical trials related to the specific drug and condition, despite status, sponsor, and outcome of a trial, as part of the marketing authorisation application?**

Yes, according to the legal requirements.

Kind regards
On behalf of

B. Michel-Lukacs

Trusted evidence. Informed decisions. Better health.

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2100 Copenhagen Ø, Denmark
Tel: +45 35 45 71 12
E-mail: general@cochrane.dk
www.nordic.cochrane.org

19 Dec 2019

Health Canada
Therapeutic Products Directorate

We are currently working on a Cochrane systematic review regarding extended-release methylphenidate for adults with attention deficit hyperactivity disorder (ADHD). The protocol for our review is available at the Cochrane Library (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012857/full).

We write to you regarding two methylphenidate formulations that your Agency has approved. If our questions and requests necessitate that we file a formal Freedom of Information Act request, please consider this letter as such a request.

Re: Osmotic-controlled release oral delivery system (OROS) methylphenidate (trade name Concerta)

Health Canada has approved the OROS-methylphenidate formulation, tradename Concerta, with Janssen as the marketing authorisation holder. According to Concerta's Drug Product Monograph, Submission Control No: 224296 (https://pdf.hres.ca/dpd_pm/00050777.PDF), the drug was approved for use in adults with ADHD based on one clinical trial (table 2.1, p. 31). We have identified the trial as NCT00246220.

We have two questions regarding the drug approval process of Concerta and two questions regarding your Agency's general drug approval procedure:

Questions regarding your Agency's approval of Concerta

1. Can you specify (year and date) when your Agency approved Concerta for use in adults with ADHD, as this is not stated in the Drug Product Monograph?

2. We are aware of other clinical trials with Concerta that, depending on the time of regulatory drug approval, would have been available for inclusion in the marketing authorisation application, see **table 1**. Did Janssen submit clinical trial data from the NCT00246220 trial only in their marketing authorisation application, or did they also include data from other Concerta trials for adults with ADHD?

Questions regarding your Agency's general drug approval procedure

3. When Janssen applied for marketing authorisation for Concerta to the British drug regulator, MHRA, the drug application included three clinical trials. In addition to the trial that your Agency assessed, Janssen included two further trials, NCT00326391 and NCT00714688, **table 1**. Based on these three trials, the MHRA did not approve Concerta for use in adults in the UK (see Public Assessment Report, http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con2033483.pdf).
   Our question is: prior to approving or rejecting a marketing authorisation application, does your Agency normally consult with other drug regulatory agencies regarding their decisions and reasoning for approval or rejection of individual drugs?

4. Does your Agency require an applicant to submit information and data about *all* available clinical trials related to the specific drug and indication, irrespective of status, sponsor, and outcome of the trial, as part of the marketing authorisation application?

Re: Extended-release methylphenidate (trade name Foquest)

In February 2018, Health Canada approved another extended-release methylphenidate formulation (trade name Foquest) for use in adults with ADHD marketed by Purdue.

We would like to file a Freedom of Information Act request for the release of the clinical trial data underlying this drug approval. We are interested in the clinical study reports (particularly module 2 and module 5 of the submitted marketing authorisation application by Purdue), the protocol, case report forms and, if Health Canada are in possession of them, the anonymised individual patient data. This data may be of great importance to our systematic review.

Please contact me if my questions or requests need further clarification.

Thank you for your help.

Sincerely,

Kim Boesen, MD
Nordic Cochrane Centre
Rigshospitalet, Dept. 7811
Blegdamsvej 9
2200 Copenhagen Ø
Denmark

Table 1. OROS-methylphenidate (Concerta) trials

Trial ID	Study start – completion	NCT entry	Published report
NCT00181571	June 2003 - Aug 2007	https://clinicaltrials.gov/ct2/show/NCT00181571	Biederman et al, 2010 (doi: 10.1097/JCP.0b013e3181ee84a7)
NCT00246220 (LAMDA-I)	Mar 2005 – Nov 2006	https://clinicaltrials.gov/ct2/show/NCT00246220	Medori et al, 2008 (doi: 10.1016/j.biopsych.2007.11.008)
NCT00326391	Apr 2006 – Dec 2006	https://clinicaltrials.gov/ct2/show/NCT00326391	Adler et al, 2009 (doi: 10.1097/JCP.0b013e3181a390ce)
NCT00714688 (LAMDA-II)	Feb 2008 - Apr 2009	https://clinicaltrials.gov/ct2/show/NCT00714688	Casas et al, 2013 (doi: 10.3109/15622975.2011.600333)
NCT00937040	July 2009 - Feb 2010	https://clinicaltrials.gov/ct2/show/NCT00937040	Goodman et al, 2016 (doi: 10.4088/JCP.15m10348)
NCT01323192	Mar 2011 - Apr 2012	https://clinicaltrials.gov/ct2/show/NCT01323192	Takahashi et al, 2014 (doi: 10.3109/15622975.2013.868925)

Legend. Data is taken from clinicaltrials.gov. The highlighted trial was included in Canada Health's Drug Product Monograph of Concerta.

CONCERTA by JANSSEN INC

Clinical Data / Données Cliniques (HC/SC) <hc.clinicaldata-donneescliniques.sc@canada.ca> Wed, Apr 22, 2020 at 5:22 PM
To: "Clinical Data / Données Cliniques (HC/SC)" <hc.clinicaldata-donneescliniques.sc@canada.ca>, "kb@cochrane.dk" <kb@cochrane.dk>

Morning,

We write in response to the request received through the Health Canada Clinical Information Portal for information on CONCERTA by JANSSEN INC.

Please confirm if you are looking for the clinical data on the study you have cited or whether you are interested in answers to your questions.

It would not be fitting for PRCI to respond to these questions as we only manage the publication of clinical information. Your email would be forwarded to the relevant review bureau.

PRCI Team

From: Health Canada - Santé Canada <hc.donotreply-nepasrepondre.sc@hc-sc.gc.ca>
Sent: 2020-04-03 8:30 AM
To: Clinical Data / Données Cliniques (HC/SC) <hc.clinicaldata-donneescliniques.sc@canada.ca>
Subject: A request for documents has been received on the PRCI public interface. | Une demande pour des documents a été reçue sur l'interface publique DPRC.

A request for documents related to CONCERTA by JANSSEN INC has been received on the PRCI public interface.

Drug Name: CONCERTA
Dosage form(s) and Route(s) of Administration: tablet
Manufacturer Name: JANSSEN INC
Indication(s) / Condition(s) of Use: Attention deficit hyperactivity disorder in adults
Submission Control Number: 224296

I am requesting information from: The initial marketing approval
I am specifically interested in: Other
Reason for Request and any additional information: We are currently working on a Cochrane systematic review regarding extended-release methylphenidate for adults with attention deficit hyperactivity disorder (ADHD). The protocol for our review is available at the Cochrane Library (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012857/full).

We write to you regarding the OROS methylphenidate formulation (trade name Concerta) that your Agency has approved. If our questions and requests necessitate that we file a formal Freedom of Information Act request, please consider this letter as such a request.

Health Canada has approved the OROS-methylphenidate formulation, tradename Concerta, with Janssen as the marketing authorisation holder. According to Concerta's Drug Product Monograph, Submission Control No: 224296 (https://pdf.hres.ca/dpd_pm/00050777.PDF), the drug was approved for use in adults with ADHD based on one clinical trial (table 2.1, p. 31). We have identified the trial as NCT00246220.

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Questions regarding your Agency's approval of Concerta
1. Can you specify (year and date) when your Agency approved Concerta for use in adults with ADHD, as this is not stated in the Drug Product Monograph?
2. We are aware of other clinical trials with Concerta that, depending on the time of regulatory drug approval, would have been available for inclusion in the marketing authorisation application, see table 1. Did Janssen submit clinical trial data from the NCT00246220 trial only in their marketing authorisation application, or did they also include data from other Concerta trials for adults with ADHD?

Questions regarding your Agency's general drug approval procedure
3. When Janssen applied for marketing authorisation for Concerta to the British drug regulator, MHRA, the drug application included three clinical trials. In addition to the trial that your Agency assessed, Janssen included two further trials, NCT00326391 and NCT00714688, table 1. Based on these three trials, the MHRA did not approve Concerta for use in adults in the UK (see Public Assessment Report, http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con203.... pdf).
Our question is: prior to approving or rejecting a marketing authorisation application, does your Agency normally consult with other drug regulatory agencies regarding their decisions and reasoning for approval or rejection of individual drugs?
4. Does your Agency require an applicant to submit information and data about all available clinical trials related to the specific drug and indication, irrespective of status, sponsor, and outcome of the trial, as part of the marketing authorisation application?

Table 1. OROS-methylphenidate (Concerta) trials
[Trial ID; Study start – completion; NCT entry; Published report]

NCT00181571; June 2003 - Aug 2007; https://clinicaltrials.gov/ct 2/show/NCT00181571; Biederman et al, 2010 (doi: 10.1097/JCP.0b013e3181ee84a7).

NCT00246220 (LAMDA-I); Mar 2005 – Nov 2006; https://clinicaltrials.gov/ct 2/show/NCT00246220; Medori et al, 2008 (doi: 10.1016/j.biopsych.2007.11.008).

NCT00326391; Apr 2006 – Dec 2006; https://clinicaltrials.gov/ct 2/show/NCT00326391; Adler et al, 2009 (doi: 10.1097/JCP.0b013e3181a390ce).

NCT00714688 (LAMDA-II); Feb 2008 - Apr 2009; https://clinicaltrials.gov/ct 2/show/NCT00714688; Casas et al, 2013 (doi: 10.3109/15622975.2011.600333).

NCT00937040; July 2009 - Feb 2010; https://clinicaltrials.gov/ct 2/show/NCT00937040; Goodman et al, 2016 (doi: 10.4088/JCP.15m10348).

NCT01323192; Mar 2011 - Apr 2012; https://clinicaltrials.gov/ct 2/show/NCT01323192; Takahashi et al, 2014 (doi: 10.3109/15622975.2013.868925).

Name of Requester: Kim Boesen
Email Address: kb@cochrane.dk
Requester category / originator: Academia
Affiliation(s): Nordic Cochrane Centre
Title: MD, PhD student

Thank you,
PRCI public interface

Une demande pour des documents reliés à CONCERTA par JANSSEN INC a été reçue sur l'interface publique DPRC

Nom du médicament: CONCERTA
Forme(s) posologique(s) et voie(s) d'administration: tablet
Nom du fabricant: JANSSEN INC
Indication(s) / Condition(s) d'utilisation: Attention deficit hyperactivity disorder in adults
Numéro de contrôle de la présentation: 224296

Je demande à obtenir des renseignements pour: Approbation initiale avant la commercialisation
Je suis particulièrement intéressé(e) par: Autre
Raison justifiant la demande et renseignements supplémentaires: We are currently working on a Cochrane systematic review regarding extended-release methylphenidate for adults with attention deficit hyperactivity disorder (ADHD). The protocol for our review is available at the Cochrane Library (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012857/full).

We write to you regarding the OROS methylphenidate formulation (trade name Concerta) that your Agency has approved. If our questions and requests necessitate that we file a formal Freedom of Information Act request, please consider this letter as such a request.

Health Canada has approved the OROS-methylphenidate formulation, tradename Concerta, with Janssen as the marketing authorisation holder. According to Concerta's Drug Product Monograph, Submission Control No: 224296 (https://pdf.hres.ca/dpd_pm/00050777.PDF), the drug was approved for use in adults with ADHD based on one clinical trial (table 2.1, p. 31). We have identified the trial as NCT00246220.

We have two questions regarding the drug approval process of Concerta and two questions regarding your Agency's general drug approval procedure:

Questions regarding your Agency's approval of Concerta
1. Can you specify (year and date) when your Agency approved Concerta for use in adults with ADHD, as this is not stated in the Drug Product Monograph?
2. We are aware of other clinical trials with Concerta that, depending on the time of regulatory drug approval, would have been available for inclusion in the marketing authorisation application, see table 1. Did Janssen submit clinical trial data from the NCT00246220 trial only in their marketing authorisation application, or did they also include data from other Concerta trials for adults with ADHD?

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Our question is: prior to approving or rejecting a marketing authorisation application, does your Agency normally consult with other drug regulatory agencies regarding their decisions and reasoning for approval or rejection of individual drugs?
4. Does your Agency require an applicant to submit information and data about all available clinical trials related to the specific drug and indication, irrespective of status, sponsor, and outcome of the trial, as part of the marketing authorisation application?

Table 1. OROS-methylphenidate (Concerta) trials
[Trial ID; Study start – completion; NCT entry; Published report]

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NCT00326391; Apr 2006 – Dec 2006; https://clinicaltrials.gov/ct 2/show/NCT00326391; Adler et al, 2009 (doi: 10.1097/JCP.0b013e3181a390ce).

NCT00714688 (LAMDA-II); Feb 2008 - Apr 2009; https://clinicaltrials.gov/ct 2/show/NCT00714688; Casas et al, 2013 (doi: 10.3109/15622975.2011.600333).

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NCT01323192; Mar 2011 - Apr 2012; https://clinicaltrials.gov/ct 2/show/NCT01323192; Takahashi et al, 2014 (doi: 10.3109/15622975.2013.868925).

Nom du demandeur: Kim Boesen
Adresse électronique: kb@cochrane.dk
Auteur / catégorie de demandeur: Secteur universitaire
Affiliation(s): Nordic Cochrane Centre
Titre: MD, PhD student

Merci,
Interface publique DPRC

CONCERTA by JANSSEN INC

Kim Boesen <kb@cochrane.dk> Mon, Apr 27, 2020 at 4:28 PM
To: "Clinical Data / Données Cliniques (HC/SC)" <hc.clinicaldata-donneescliniques.sc@canada.ca>

Dear PRCI team,

Thank you for your email. I am interested in getting my questions answered, so I would appreciate very much if you can forward them to the relevant review bureau.

Thanking you in advance.

Sincerely,
Kim Boesen
[Quoted text hidden]
--
Kim Boesen, MD
Researcher
Nordic Cochrane Centre

CONCERTA by JANSSEN INC

Clinical Data / Données Cliniques (HC/SC) <hc.clinicaldata-donneescliniques.sc@canada.ca> Tue, Apr 28, 2020 at 1:37 PM
To: Kim Boesen <kb@cochrane.dk>, "Clinical Data / Données Cliniques (HC/SC)" <hc.clinicaldata-donneescliniques.sc@canada.ca>

Morning,

We write to inform you that your email was sent to The Therapeutic Products Directorate, Director General's Office hc.dgo.tpd-bdg.dpt.sc@canada.ca and they will follow up with an answer.

Regards,

PRCI Team.

From: Kim Boesen <kb@cochrane.dk>
Sent: 2020-04-27 10:29 AM
To: Clinical Data / Données Cliniques (HC/SC) <hc.clinicaldata-donneescliniques.sc@canada.ca>
Subject: Re: CONCERTA by JANSSEN INC

Dear PRCI team,

Thank you for your email. I am interested in getting my questions answered, so I would appreciate very much if you can forward them to the relevant review bureau.

Thanking you in advance.

Sincerely,

Kim Boesen

[Quoted text hidden]

--

[Quoted text hidden]

FW: CONCERTA by JANSSEN INC

BCANS Enquiries (HC/SC) <hc.bcansenquiries.sc@canada.ca> Fri, Jun 19, 2020 at 6:51 PM
To: "kb@cochrane.dk" <kb@cochrane.dk>

Dear Kim Boesen,

Thank you for contacting Health Canada on April 4, 2020, with your request for information related to the authorization of CONCERTA for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adults and your questions regarding Health Canada's drug approval framework.

Please see below for answers to your questions.

1. Can you specify (year and date) when your Agency approved Concerta for use in adults with ADHD, as this is not stated in the Drug Product Monograph?

The Notice of Compliance (NOC) for CONCERTA was issued on April 15, 2008, for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in **adults**.

2. We are aware of other clinical trials with Concerta that, depending on the time of regulatory drug approval, would have been available for inclusion in the marketing authorisation application, see table 1. Did Janssen submit clinical trial data from the NCT00246220 trial only in their marketing authorisation application, or did they also include data from other Concerta trials for adults with ADHD?

Please see the attached document for the list of studies provided by Janssen in their submission for the addition of CONCERTA's adult indication.

3. When Janssen applied for marketing authorisation for Concerta to the British drug regulator, MHRA, the drug application included three clinical trials. In addition to the trial that your Agency assessed, Janssen included two further trials, NCT00326391 and NCT00714688, table 1. Based on these three trials, the MHRA did not approve Concerta for use in adults in the UK (see Public Assessment Report, http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con203.... pdf).
Our question is: prior to approving or rejecting a marketing authorisation application, does your Agency normally consult with other drug regulatory agencies regarding their decisions and reasoning for approval or rejection of individual drugs?

Health Canada, when making a decision, uses all available information, including foreign assessment reports and decisions when available. It should be noted however, that Health Canada makes an independent final decision on authorization.

4. Does your Agency require an applicant to submit information and data about all available clinical trials related to the specific drug and indication, irrespective of status, sponsor, and outcome of the trial, as part of the marketing authorisation application?

Health Canada expects that all trials related to the indication, regardless of outcome, should be submitted as part of the submission. When a sponsor files a submission with Health Canada, a Submission Certification Form must be provided within the submission package. The Submission Certification Form confirms that all the information and material included in the submission and additional information or material filed to amend the submission are accurate and complete. By signing this form, the sponsor also confirms that no information is false or misleading and that no omissions have been made that may affect its accuracy and completeness.

Kinds regards,

Bureau of Cardiology, Allergy and Neurological Sciences

BCANS Enquiries / Government of Canada

HC.bcans.enquiries.SC@canada.ca / Tel: 613-941-1499 / Fax: 613-941-1668

Bureau de cardiologie, allergologie et sciences neurologiques

Enquêtes BCASN / Gouvernement du Canada

HC.bcans.enquiries.SC@canada.ca / Tél. : 613-941-1499 / Télé. : 613-941-1668

From: Kim Boesen <kb@cochrane.dk>
Sent: 2020-04-27 10:29 AM

To: Clinical Data / Données Cliniques (HC/SC) <hc.clinicaldata-donneescliniques.sc@canada.ca>
Subject: Re: CONCERTA by JANSSEN INC

Dear PRCI team,

Thank you for your email. I am interested in getting my questions answered, so I would appreciate very much if you can forward them to the relevant review bureau.

Thanking you in advance.

Sincerely,

Kim Boesen

On Wed, Apr 22, 2020 at 5:22 PM Clinical Data / Données Cliniques (HC/SC) <hc.clinicaldata-donneescliniques.sc@canada.ca> wrote:

> Morning,
>
> We write in response to the request received through the Health Canada Clinical Information Portal for information on CONCERTA by JANSSEN INC.
>
> Please confirm if you are looking for the clinical data on the study you have cited or whether you are interested in answers to your questions.
>
> It would not be fitting for PRCI to respond to these questions as we only manage the publication of clinical information. Your email would be forwarded to the relevant review bureau.
>
> PRCI Team
>
> ---
>
> **From:** Health Canada - Santé Canada <hc.donotreply-nepasrepondre.sc@hc-sc.gc.ca>
> **Sent:** 2020-04-03 8:30 AM
> **To:** Clinical Data / Données Cliniques (HC/SC) <hc.clinicaldata-donneescliniques.sc@canada.ca>
> **Subject:** A request for documents has been received on the PRCI public interface. | Une demande pour des documents a été reçue sur l'interface publique DPRC.
>
> A request for documents related to CONCERTA by JANSSEN INC has been received on the PRCI public interface.
>
> Drug Name: CONCERTA
> Dosage form(s) and Route(s) of Administration: tablet
> Manufacturer Name: JANSSEN INC
> Indication(s) / Condition(s) of Use: Attention deficit hyperactivity disorder in adults
> Submission Control Number: 224296
>
> I am requesting information from: The initial marketing approval
> I am specifically interested in: Other
> Reason for Request and any additional information: We are currently working on a Cochrane systematic review regarding extended-release methylphenidate for adults with attention deficit hyperactivity disorder (ADHD). The protocol for our review is available at the Cochrane Library (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012857/full).
>
> We write to you regarding the OROS methylphenidate formulation (trade name Concerta) that your Agency has approved. If our questions and requests necessitate that we file a formal Freedom of Information Act request, please consider this letter as such a request.
>
> Health Canada has approved the OROS-methylphenidate formulation, tradename Concerta, with Janssen as the marketing authorisation holder. According to Concerta's Drug Product Monograph, Submission Control No: 224296 (https://pdf.hres.ca/dpd_pm/00050777.PDF), the drug was approved for use in adults with ADHD based on one clinical trial (table 2.1, p. 31). We have identified the trial as NCT00246220.
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> We have two questions regarding the drug approval process of Concerta and two questions regarding your Agency's general drug approval procedure:
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> Questions regarding your Agency's approval of Concerta
> 1. Can you specify (year and date) when your Agency approved Concerta for use in adults with ADHD, as this is not stated in the Drug Product Monograph?
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Questions regarding your Agency's general drug approval procedure
3. When Janssen applied for marketing authorisation for Concerta to the British drug regulator, MHRA, the drug application included three clinical trials. In addition to the trial that your Agency assessed, Janssen included two further trials, NCT00326391 and NCT00714688, table 1. Based on these three trials, the MHRA did not approve Concerta for use in adults in the UK (see Public Assessment Report, http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con203.... pdf).
Our question is: prior to approving or rejecting a marketing authorisation application, does your Agency normally consult with other drug regulatory agencies regarding their decisions and reasoning for approval or rejection of individual drugs?
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Table 1. OROS-methylphenidate (Concerta) trials
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NCT01323192; Mar 2011 - Apr 2012; https://clinicaltrials.gov/ct 2/show/NCT01323192; Takahashi et al, 2014 (doi: 10.3109/15622975.2013.868925).

Name of Requester: Kim Boesen
Email Address: kb@cochrane.dk
Requester category / originator: Academia
Affiliation(s): Nordic Cochrane Centre
Title: MD, PhD student

Thank you,
PRCI public interface

Une demande pour des documents reliés à CONCERTA par JANSSEN INC a été reçue sur l'interface publique DPRC

Nom du médicament: CONCERTA
Forme(s) posologique(s) et voie(s) d'administration: tablet
Nom du fabricant: JANSSEN INC
Indication(s) / Condition(s) d'utilisation: Attention deficit hyperactivity disorder in adults
Numéro de contrôle de la présentation: 224296

Je demande à obtenir des renseignements pour: Approbation initiale avant la commercialisation
Je suis particulièrement intéressé(e) par: Autre
Raison justifiant la demande et renseignements supplémentaires: We are currently working on a Cochrane systematic review regarding extended-release methylphenidate for adults with attention deficit hyperactivity disorder (ADHD). The protocol for our review is available at the Cochrane Library (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012857/full).

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NCT00714688 (LAMDA-II); Feb 2008 - Apr 2009; https://clinicaltrials.gov/ct 2/show/NCT00714688; Casas et al, 2013 (doi: 10.3109/15622975.2011.600333).

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Nom du demandeur: Kim Boesen
Adresse électronique: kb@cochrane.dk
Auteur / catégorie de demandeur: Secteur universitaire
Affiliation(s): Nordic Cochrane Centre
Titre: MD, PhD student

Merci,
Interface publique DPRC

--

Kim Boesen, MD

Researcher

Nordic Cochrane Centre

2.7.6 CONCERTA 113986.docx
39K

MODULE 2.7 – CLINICAL SUMMARY

2.7.6

SYNOPSES OF INDIVIDUAL STUDIES

Issue/Report Date: 27 April 2007
Department: Regulatory Affairs

Confidentiality Statement

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you that is indicated as privileged or confidential.

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Synopsis for Clinical Study C-99-018-00 19

Tabular Listing of All Studies – CONCERTA (methylphenidate hydrochloride)

Study Number[a] Principal Investigator (Country) Start/End Dates	Study Description/Design	Subjects Evaluated[b] Sex (M/F) Age (yr): median [mean] (range) Race W/B/O	Treatment Regimen/Duration Route of Administration Batch/Formulation Numbers	Study Status Type of Report Location of Study Report or Publication
Healthy Subject PK and Initial Tolerability Studies				
02-160 EDMS-PSDB-6339671 M. Stayman (USA) Clinical phase: Start: 20 January 2003 End: 14 February 2003 Analytical phase: Start: 04 February 2003 End: 24 March 2003	Four-period, four treatment, open-label, multiple-dose, dose escalation study to determine PK and safety in healthy adults.	27 20M/7F [28.9] (20-50) 22/1/4	Sequentially increasing doses of 54 mg, 72 mg, 108 mg and 144 mg once daily x 4 days with 3-day washout between treatment periods Oral *Batch Nos:* 36 mg tablets: 0215751 54 mg tablets: 0215755	Completed Full report Mod. 5.3.3.1, v 1-16

Key: F = female; M = male; W = white; B = black; O = other
[a] The sponsor is McNeil Consumer & Specialty Pharmaceuticals
[b] Number of subjects evaluated for safety

Tabular Listing of All Studies – CONCERTA (methylphenidate hydrochloride)

Protocol Number Study Identifier[a] Principal Investigator (Country) Start/End Dates	Study Description/ Design	Subjects Evaluated [b] Sex (M/F) Age (yr): median [mean] (range) Race W/O[c]	Treatment Regimen/Duration Route of Administration Batch/Formulation Numbers	Study Status Type of Report Location of Study Report or Publication
Controlled Clinical Studies Relevant to the Proposed Indication				
42603ATT3002 EDMS-PSDB-5043916 Multicentre (Europe) Start: 07 April 2005 End: 01 August 2006	Randomized, multicentre, double-blind, placebo-controlled, parallel group, dose-response study of safety and efficacy followed by an open-label extension	401 218M/183F 34.0 [34.0] (18-63) 391/10	Double-blind phase Fixed doses of 18 mg, 36 mg or 72 mg once daily/5 weeks Oral *Batch Nos:* 18 mg: 0009478/0410815, 0009478/0413859 36 mg: 0009477/0413862, 0009477/0509380 Placebo: 0015065/12150.1 Open-label phase Flexible dosing from 18 mg to 90 mg once daily/7 weeks *Batch Nos:* 18 mg tablets: 0009478/0410815, 0009478/0509369 36 mg tablets: 0009477/0413862, 0009477/0415973, 0009477/0522184 54 mg tablets: 0009989/0412349, 0014585/0435317, 0009989/0520664, 0009989/0533009	Completed Full report Mod 5.3.5.1, v 17-53

Key: F = female; M = male; W = white; O = other
[a] The sponsor is Janssen-Cilag Medical Affairs EMEA
[b] number of subjects evaluated for safety
[c] Other is defined as 'Black or African heritage', 'Hispanic' and 'Other'

Tabular Listing of All Studies – CONCERTA (methylphenidate hydrochloride)

Protocol Number Study Identifier[a] Principal Investigator (Country) Start/End Dates	Study Description/Design	Subjects Evaluated [b] Sex (M/F) Age (yr): median [mean] (range) Race W/B/O[c]	Treatment Regimen/Duration Route of Administration Batch/Formulation Numbers	Study Status Type of Report Location of Study Report or Publication
Uncontrolled Clinical Studies				
CON-CAN-4 EDMS-PSDB-6373933 A. Fallu (Canada) Start: 29 March 2005 End: 01 December 2005	Open-label to evaluate safety, tolerability and effectiveness	32 18M/14/F 40 [36.8] (19-54) 31/1/0	Flexible doses of 18 mg to 72 mg once daily/38 days Oral *Batch Nos:* 18 mg tablets: 0422606 36 mg tablets: 0424620 54 mg tablets: 0432377	Completed Synoptic report Mod 5.3.5.2, v 54
C-99-018-00[d] EDMS-PSDB-6087123 Multicentre (USA) Start: 08 Jan 00 End: 09 Feb 01	Open-label, multicentre, non-randomized study to evaluate long-term safety, effectiveness, and clinical use	136 88M/48F [37.4] (18-66) 134/1/1	Flexible doses of 18 mg to 54 mg once daily for up to 9 months Oral *Batch Nos:* 18 mg tablets: MV9804932 36 mg tablets: MV9901498	Completed Full report Mod 5.3.5.2, v 55-76

Key: B = black; CON = CONCERTA; F = female; M = male; W = white; O = other
[a] The sponsor for CON-CAN-4 is Janssen-Ortho Inc. and for C-99-018-00 is ALZA Corporation.
[b] number of subjects evaluated for safety
[c] Other =hispanic
[d] Study included subjects =6 years of age. Data for adult subjects only is included in this table.