

Methylphenidate for ADHD rejected from the WHO Essential Medicines List due to uncertainties in benefit-harm profile

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Abstract

Attention deficit hyperactivity disorder (ADHD) is a common psychiatric disorder with estimated global prevalence rates between 3% and 5% in children and 2.5% in adults, depending on the classification system used. The psychostimulant methylphenidate is one of the most frequently used medications for ADHD. In this analysis article we describe shortly the evidence in the field, an application for inclusion of methylphenidate on the WHO Model List of Essential Medicines, the comments raised to the application and the WHO Expert Committee's decision. The application of getting methylphenidate on the WHO list was overzealous in reporting potential benefits, without highlighting key uncertainties and harms. Decisions encompassing medicines candidate to the WHO Model List should not be based on speculation about potential benefits and should fully incorporate areas of uncertainties. Even though methylphenidate has been used for over 60 years, the evidence concerning the benefits of this medication in children, adolescents and adults with ADHD is uncertain. The decision of the committee was to not include methylphenidate in the WHO Model List of Essential Medicines 'due to uncertainties in the estimates of benefit, and concerns regarding the quality and limitations of the available evidence for both benefit and harm'.

Background

Attention deficit hyperactivity disorder (ADHD) is a common psychiatric disorder with estimated global prevalence between 3% and 5% in children and about 2.5% in adults, depending on the classification system used.¹⁻³ Diagnosis is based on one or more of the following symptoms: excessive inattention, hyperactivity and impulsivity, and symptoms must interfere with everyday life before the age of 7 (International Classification of Diseases-10) or 12 years (Diagnostic and Statistical Manual of Mental Disorders-5).^{4,5} Children, adolescents and adults with ADHD are at increased risk of a broad spectrum of co-occurring conditions.^{6,7} The Multimodal Treatment of ADHD trial identified one or more co-occurring disorders in almost 40% of the participants, including oppositional defiant disorder, conduct disorder, depression, anxiety, tics, learning disorders, and verbal and cognitive difficulties.⁸

What does the evidence show?

The psychostimulant methylphenidate is one of the most frequently used medications to treat ADHD.⁹ Even though methylphenidate has been used for over 60 years for this indication, the evidence concerning the benefits and harms of this medication in children, adolescents and adults with ADHD remains uncertain.¹⁰⁻¹⁶ Several studies have shown a possible favourable effect on ADHD symptoms, but the true magnitude of this effect is unknown.¹⁰⁻¹⁶

In spite of these findings, a network meta-analysis from 2018 concluded that there is sufficient evidence to support short-term use within 12 weeks of methylphenidate in both children and adults, and so far there are no trials investigating the effects beyond the 12-week treatment period or close to that.¹⁷ Some methodological problems with the network meta-analysis should be mentioned. Selection and assessment bias may have confounded the results because the authors excluded many relevant trials and ignored bias from lack of fair comparator.¹⁷ The participants in the medication groups could have been subject to systematic unblinding, given the known adverse events of ADHD medications compared with placebo interventions.¹⁸ Here both the adverse effects in the experimental group and lack of adverse effects in the placebo group may lead to deblinding. Blinding is normally ensured by designing externally identical experimental and control interventions, often with a placebo control that matches the colour, smell, texture, taste and solubility of the experimental intervention. However, standard placebos do not control for noticeable psychotropic effects or adverse effects of the experimental intervention. There are many challenges to this as active placebos induce adverse effects in trial participants that they would otherwise not experience. There is also a theoretical risk of an unintended therapeutic effect on the trial outcome, and appropriate active placebos may be difficult to construct. The problem of adequate comparator was raised as early as 1958,¹⁹ and has since been discussed sporadically in the scientific literature, mostly in the context of trials of antipsychotics and antidepressants.²⁰⁻²² More recently, it has also been raised for trials of methylphenidate for ADHD.^{10,13-15} Moreover, very few adverse events were assessed in the network meta-analysis, which is a clear methodological drawback.

The National Institute for Health and Care Excellence (NICE) guideline recommends

methylphenidate as the first-line pharmacological treatment for children over 5 and adolescents.²³ The NICE guideline committee concludes that methylphenidate and lisdexamfetamine provide clinically important benefits to patients with ADHD as compared with placebo and other drugs.²³ However, a closer look at the NICE guideline reveals several methodological problems, which especially involves an erratic assessment of the certainty of the included studies. In the assessment of the effect of methylphenidate, they only included 16 trials on methylphenidate in children and adolescents. We included 185 trials (of which 175 were placebo-controlled) in our systematic review from 2015 by searching many databases.¹⁵ We and the NICE guideline did not search the web pages from the European Medicines Agency (EMA) and the Food and Drug Administration (FDA), so we may have missed unpublished studies.

NICE did not adjust for multiple comparisons in their analyses and they did not discuss the concern that all the data were assessed during a short-term follow-up.¹² In an article describing the clinical practice guideline for the diagnosis, evaluation and treatment of ADHD in children and adolescents published in *Pediatrics* in 2019,²⁴ the guideline strongly recommends pharmaceutical treatments (US FDA-approved medications for ADHD) together with evidence-based behavioural interventions to schoolchildren and adolescents with ADHD. The guideline states that there is a strong effect observed in the trials investigating the effects of stimulant medications. However, the authors describe that despite an enormous research effort, there are several gaps in the knowledge base, and several questions concerning the quality of evidence exist. The issues concern the uncertainties of long-term evidence and safety as well as the comparative effectiveness of different medications.²⁴

Some observational studies suggest a protective effect of stimulants on risk of injuries and criminality. A Swedish national register study, including 25 656 participants, suggested that treatment with medications for ADHD led to 32% and 41% reduction in criminality among men and women, respectively.²⁵ In another observational study, the authors found that ADHD was associated with an increase in serious transport accidents and that sufficient treatment with ADHD medication seemed to reduce this risk by approximately 58%, especially in male patients.²⁶ There have also been reports suggesting a reduction in motor vehicle accidents when patients were treated with methylphenidate.²⁷ These are all well-done observational studies that may give information about the possible effect of stimulants. However, these studies are all non-randomised, and there are therefore risks for confounding factors, other errors or random errors. In such studies, there is a significant risk that the relationship one observes—for example, between medication and a lower risk of crime or accidents in the two studies above^{25 26}—might in fact be due to other factors that have not been taken into consideration. In within-individual design studies, participants are compared with themselves and one can therefore better exclude alternative explanations of the difference between periods with and without prescriptions. But then new problems arise that can create uncertainty about the real effect, for instance that in some cases there is quite a long time between when people are diagnosed with ADHD and the time when they receive a verdict for a crime or get in an accident. During that period, the only knowledge one has about their behaviour is information from the records of whether or not they have been prescribed the medication. Therefore, the researchers have very little control over whether people have actually taken the medication during the periods they are prescribed the medication. In a randomised clinical trial, researchers usually monitor

whether the participants adhere to the treatment and take medication.

In a new placebo discontinuation trial by Matthijsen *et al*,²⁸ 94 children and adolescents were randomly assigned to double-blind continuation of treatment for 7 weeks or to gradual withdrawal over 3–5 weeks of placebo. Before this, the children and adolescents had been administered methylphenidate for more than 2 years. The primary outcome was the clinician-rated ADHD Rating Scale (ADHD-RS). The secondary outcome was Clinical Global Impressions Improvement (CGI-I) scale. The mean difference in change over time was -4.6 (95% CI -8.7 to -0.56) on the ADHD-RS. The CGI-I indicated worsening in 40.4% of the discontinuation group, compared with 15.9% of the continuation group. This trial supports that long-term methylphenidate is effective; however, a closer look at the ADHD-RS change shows that this difference is not above the minimal clinically relevant difference of ADHD-RS of -6.6 points.²⁹ It is also interesting that approximately 60% in the discontinuation group did not get worse. The placebo withdrawal trial consists of a starting phase where patients who are openly treated with the medication are evaluated. In the second phase, participants who have responded well to medication are randomly assigned to continue the same treatment or switch to placebo. Those who show adverse reactions to methylphenidate are excluded from such trials. There are advantages to the placebo discontinuation trials, and one of these is that they are recommended by EMA.³⁰ However, we believe that the placebo withdrawal trials are not very well suited to estimate the magnitude of absolute treatment effects as they do it in a select group of patients.³¹ Because well-conducted randomised clinical trials are lacking, it remains unclear whether the abovementioned results constitute real benefits or statistical artefacts.³² For adverse events associated with the treatment, systematic reviews of randomised clinical trials and of non-randomised studies demonstrated uncertainty about serious adverse events and a high proportion of participants suffering from a range of non-serious adverse events.^{14 15}

The application to the WHO Model List

In December 2018, Patricia Moscibrodzki and Craig L Katz from the Icahn School of Medicine at Mount Sinai, Graduate Program in Public Health in New York, New York, USA applied to add methylphenidate to the WHO Model List of Essential Medicines.³³ The application was 60 pages long and provided a review of the use, efficacy, safety, availability and cost-effectiveness of methylphenidate compared with other stimulant (first-line) and non-stimulant (second-line) medications. The application was for all age groups.

Moscibrodzki and Katz stated that methylphenidate has been consistently proven to have superior ranking in efficacy and tolerability than other medications, and with fewer reported adverse effects. They subsequently argued that methylphenidate should be included in the complementary list of the WHO Model List of Essential Medicines for the treatment of ADHD. The complementary list presents medicines that are mostly prescribed by specialists, and often require specialised diagnostic or monitoring facilities, as opposed to the core list which presents medicines used in primary care settings. The application included 28 studies and review articles as evidence for the comparative effectiveness of methylphenidate for the treatment of ADHD. The comparators were placebo or other stimulants, and second-line non-stimulant therapies. The majority of the trials and reviews were conducted in children and adolescents with ADHD and other co-occurring conditions and were short in duration—below 12 weeks.

The application did not include assessment of the quality of the evidence or confidence in the certainty of estimates of benefit.⁵³³

The public comments

The application received five recommendation letters (presented as an appendix to the document). One from Dr Sandip Shah, Professor and Head of the Department of Psychiatry at GMERS Medical College and Hospital in Vadodara, India, and one from the Ministry of Health in Belize, Central America, as well as three letters of recommendations from the Ministry of Health in Grenada.

One further public comment was written by us.⁵³⁴ We were concerned about the trustworthiness of parts of the application, as we found important limitations in the way the evidence was reported and summarised.^{533 534} Our comment focused on the following four points: the quality of the evidence, the duration of trials, misplacement of evidence and strong suspicion of strategic use of selective bias.⁵³⁴ First, it was striking that the applicants did not mention the quality of the evidence for methylphenidate (Summary of the Comparative Effectiveness of Methylphenidate in a Variety of Clinical Settings).⁵³⁴ They referred to our Cochrane systematic review published in 2015,¹⁵ which reported the observed methylphenidate effect sizes in children and adolescents with ADHD, without highlighting any concerns we made about the quality of the evidence. Our conclusion in the review was: 'The results of meta-analyses suggest that methylphenidate may improve teacher-reported ADHD symptoms, teacher-reported general behaviour, and parent-reported quality of life among children and adolescents diagnosed with ADHD. However, the low quality of the underpinning evidence means that we cannot be certain of the magnitude of the effects.'¹⁵ Moreover, another Cochrane review on methylphenidate for adults with ADHD had to be withdrawn after severe critique of its quality, as well as the quality of the included trials.^{11 535} These uncertainties prevent any firm conclusions about methylphenidate therapeutic role in ADHD at present.

Furthermore, an important Cochrane systematic review on amphetamines for children and adolescents with ADHD⁵³⁶ was not reported in the application to the WHO. The authors of this Cochrane systematic review wrote that amphetamines might be beneficial in improving ADHD core symptoms, but that most of the included studies were at high risk of bias and the overall quality of the evidence ranged from very low to low in most outcomes. Amphetamines were also associated with several adverse events.⁵³⁶ In the WHO application chapter describing the evidence for methylphenidate for adults, there seems to be, again, some selectivity in the sources or constructs cited, omitting all threats to internal and external validity of studies assessing methylphenidate. The Cochrane reviews on methylphenidate or amphetamines for adults with ADHD were silenced.^{11 535 537} Nothing was mentioned about the very short duration of the trials. There were almost no trials on the benefits (and harms) of methylphenidate in children, adolescents and adults with ADHD with duration above 3 months, a length of time which is necessary to understand the value of methylphenidate in clinical practice.^{15 538}

Another Cochrane systematic review on observational studies on methylphenidate and adverse events in children and adolescents with ADHD was wrongly quoted into the chapter dealing with adults.¹⁴ Here, the authors suddenly describe the quality of evidence.⁵³³ They wrote that the evidence was of very low quality. We agree with that. However, they wrote that it is not possible to accurately estimate the actual risk of adverse events due to the

very low quality of the evidence. Their interpretation does not seem to be correct. As we wrote in the review:

Our findings suggest that methylphenidate may be associated with a number of serious adverse events as well as a large number of non-serious adverse events in children and adolescents, which often lead to withdrawal of methylphenidate. Our certainty in the evidence is very low, and accordingly, it is not possible to accurately estimate the actual risk of adverse events. It might be higher or lower than reported here.¹⁴

In the discussion section of the review, we further wrote: 'High risk of bias in randomised clinical trials has been shown to overestimate benefits and underestimate harms, and this is especially common in trials funded by industry'.^{14 539} Our assessment of the evidence supporting methylphenidate for ADHD and other disorders is much more critical than expressed by Moscibrodzki and Katz.⁵³³ Due to the high risks of bias of all randomised clinical trials, positive intervention effects are likely to be overestimated and risks of harms are likely to be underestimated.^{15 18}

Because methylphenidate has many easily recognisable adverse events observed during treatment, which thereby make it possible for participants and assessors to guess which treatment children are receiving, we do not believe that we can obtain an objective, unbiased assessment of methylphenidate before randomised clinical trials are conducted with proper blinding through the use of a nocebo (active placebo).^{15 18}

We therefore questioned the place of methylphenidate hydrochloride on any essential list of medicines before such trials are conducted and solid evidence for more benefits than harms is established through new systematic reviews comparing methylphenidate with a proper nocebo.

The WHO Expert Committee decision

The decision by the WHO Expert Committee was to reject the application: 'The Expert Committee did not recommend the addition of methylphenidate to the complementary list of the Essential Medicine List (EML) and Essential Medicine List children (EMLc) for the treatment of attention-deficit hyperactivity disorder (ADHD) due to concerns regarding the quality and interpretation of the evidence for benefits and harms'.⁵⁴⁰ The decision was unanimous.

What should we do in the light of the uncertainty of the evidence?

The decision by the Expert Committee reflects the actual uncertainty surrounding the role of methylphenidate in ADHD. We have in many articles argued that the evidence base for the use of methylphenidate for children and adolescents with ADHD is very weak.¹² Not everyone agrees with us on this,¹⁶ but almost all researchers and clinicians agree that there is no evidence for neither the benefits or harms from randomised clinical trials with a duration exceeding 12 weeks. This is very problematic as ADHD is considered a chronic condition⁵⁴¹ and most patients are treated for years.²⁴

The existing trials on the benefits and harms of methylphenidate for ADHD have methodological issues. We must improve our clinical research base through well-powered, methodologically rigorous trials, with a focus on both benefits and harms. It is also important to secure blinding (eg, use of an 'active' placebo) to control for the adverse events in methylphenidate, a priori protocols that reduce publication bias and actions to reduce financial conflicts of interests.

Additional references can be found in online supplementary file 1.

Contributors OJS wrote the first draft. Both authors approved the final version. OJS is the guarantor. The contributors are scientists with a long-standing interest in the treatment of ADHD.

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