EBM analysis

Methylphenidate denied access to the WHO List of Essential Medicines for the second time

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Introduction

Attention deficit hyperactivity disorder (ADHD) is a common psychiatric disorder with estimated prevalence between 3% and 5% in children and about 2.5% in adults.[1] The prevalence varies across countries and even regions within the same country.[2] The psychostimulant methylphenidate is used as the first-line treatment for ADHD in children, adolescents and adults in many countries.[3]

Essential medicines are those that satisfy the priority healthcare needs of the majority of the population and, as such, should be available in a functioning healthcare system at all times. This concerns the availability of appropriate dosages, amounts and quality. The costs of an essential medicine should be set at a level, which is affordable to the individual in a given community. To ensure low costs, sufficient supply and rational use of essential medicines, the World Health Organization (WHO) created the first Model List of Essential Drugs in 1977 (now Model List of Essential Medicines). The list has since then been updated 22 times, most recently in September 2021.[4] The selection of a medication as an essential medicine should be based on its relevancy to disease patterns, the quality and cost-effectiveness of the medicine, its pharmacokinetics and acceptability, notwithstanding the evidence of its performance in a variety of settings as well as evidence of its efficacy and safety.[5]

For the 21st update of the WHO Model List in 2018, an application was submitted by researchers from Mount Sinai Graduate Programme in Public Health to include methylphenidate on the list as an essential medicine for children, adolescents and adults with ADHD. The 2018 application had several deficiencies, which has been covered elsewhere.[6] The application was rejected by the WHO Expert Committee due to concerns regarding the quality and interpretation of the evidence for benefits and harms. The same research team made a comparable application in 2020 for the 22nd update of the list. The decision of the committee was—for the second time—not to include methylphenidate in the WHO Model List of Essential Medicines 'due to uncertainties in the estimates of benefit of the medication'.

This article summarises the main points in the application and the justifications by peer reviewers that led to rejection of its request.

Applicants

The President of the World Federation of ADHD, Stephen V Faraone, is the first author of the application. Additional contributing authors are Tobias Banaschewski, David Coghill, Samuele Cortese, Jeffrey H Newcorn, Craig L Katz and Patricia Moscibrodzki. The latter was also an author of the application submitted in 2018. Stephen V Faraone, Tobias Banaschewski, David Coghill and Jeffrey H Newcorn are affiliated with several pharmaceutical companies and have been receiving support and fees from these in different contexts and over several years. Samuele Cortese, Craig L Katz and Patricia Moscibrodzki reported no conflicts of interest.

Content of the application

The 2020 application initiates with a summary statement of the proposal for inclusion of methylphenidate on the WHO List of Essential Medicines. Next, there are chapters describing the organisations supporting the application and the international names of methylphenidate as well as appropriate doses, which the application proposes for inclusion. There is a brief chapter stating the request that methylphenidate be listed as a representative of a pharmacological class rather than an individual medicine. The application then proceeds with chapters on treatment details, the public health relevance of methylphenidate, reviews of benefits and harms, and the cost-effectiveness of methylphenidate. Finally, there is a summary of the regulatory status and availability of methylpehidate.[7] In the summary statement of the application, the authors refer to a review by the European ADHD Guidelines Group as being the most comprehensive meta-analysis of short-term randomised clinical trials. The authors of the application claim that this review proves methylphenidate to be beneficial in the short term for children, adolescents and adults.[8] There are, however, some methodological problems with this review, which have been described in a letter to *The Lancet Psychiatry*.[9] The discussion regarding these methodological issues was not included in the application.

The application makes referrals to large observational registry studies claiming that methylphenidate reduces accidental injuries, traumatic brain injury, substance abuse, cigarette smoking and many other outcomes. However, the replacement

of randomised trials with non-randomised studies is not a good or safe solution due the high risk of unmeasured confounding factors in such studies.[10] Throughout the application, there is a paucity of nuance in the discussion of the central evidence.

In the previous application from 2018, the WHO Expert Committee relied on conclusions from Storebø *et al*.[11] In the current application, the authors refer to this as problematic. They claim that

> ...that meta-analysis is flawed due to its use of idiosyncratic methods to assess the quality of the evidence and factual errors, such as inappropriate study inclusion, incorrect downgrading of the evidence based on the GRADE system, and incorrect data imputation. (7 pp 6-7 (Application)).

Through several articles it has been argued and established that the meta-analyses in Storebø *et al* are not flawed.[6 12] Unfortunately, these arguments have been omitted from the application.

The application describes methylphenidate as the recommended first-line treatment for ADHD in many guidelines including the National Institute for Healthcare and Excellence (NICE) guideline.[13] The NICE recommendations on pharmacological treatments for ADHD are, however, informed by systematic reviews with serious methodological limitations and low-certainty studies.[14] These aspects are not discussed in the application. Meanwhile, the authors list conclusions from other newer reviews as arguments for the benefits of methylphenidate. In a recent viewpoint, however, we assessed 24 reviews and meta-analyses on methylphenidate for children and adolescents with ADHD published after 2015.[15] Here, we showed that the included evidence claiming a beneficial effect of methylphenidate was of very low certainty.[15]

Overall, this current application is comprehensive and seems to include all evidence in the field regarding both benefits and harms. There is, however, no discussion of the risk of epileptic seizures in the application. Man *et al* found that there is an increased risk of seizure during the first 30 days of methylphenidate treatment.[16] The authors of the application report from the International Consensus Statement on ADHD that children treated with methylphenidate show a reduced height velocity averaging 2 cm over 1 or 2 years.[3] The application also mentions the risk that dependence and/or abuse may develop and the risk that tolerance to therapeutic effects may develop in some patients. The risk of adverse effects and hereby the prudency of periodic monitoring of weight, blood pressure, platelet counts and liver function are similarly discussed.

Summary of the peer reviews

There are currently no medicines for ADHD on the WHO List of Essential Medicines.[7] Several other medicines for the treatment of ADHD are on the market and have been compared with methylphenidate.[17] Both peer reviewers agree that the application does not adequately address the issue of public health needs for methylphenidate. One reviewer points to the worldwide prevalence of ADHD throughout a decade as being consistent and, as such, does not indicate a public health need.[7] Another reviewer points out the applications' lack of evidence for ADHD prevalence, which makes proper assessment of public health significance and consequences difficult. Furthermore, the conflicts of interest in the main reference by the World Federation for Attention Deficit Hyperactivity Disorder (which is the organisation that has submitted the application) are suggested as potentially problematic. Both peer reviewers agree that all relevant evidence has been included in the application and that evidence of adverse effects associated with methylphenidate has been adequately provided. Both reviewers, however, also state that there are adverse effects of concern with the use of methylphenidate, which may require special monitoring, i.e, growth suppression, changes in weight, cardiovascular risks such as increased heart rate and blood pressure, as well as substance abuse.[7] Both peer reviewers mention the paucity of trials beyond 12 weeks and the quality of the evidence on methylphenidate as insufficient to determine risks:

> The quality of the overall evidence does not allow to determine the overall absolute risk of the medicine. The absence of sufficient data on long-term treatment is also an obstacle to determining risks. (7 p 2 (Peer reviewer 2)).

Moreover, one peer reviewer points out the inadequacy of assessing adverse effects with an offset in randomised clinical trials, as larger samples are required to identify adverse effects. Attention is also given to the difference between adverse effects and the tolerability proportion of participants dropping out of trials due to adverse events and effects. One reviewer mentions that the authors of the application refer to publications where in several cases they themselves are authors; hence, the potential conflict of interest is pointed out. The application rests on the interpretations from the network meta-analysis by Cortese and colleagues where the ADHD medicines amphetamines, atomoxetine, bupropion, clonidine, guanfacine, methylphenidate and modafinil were compared with each other or placebo to determine efficacy. It is highlighted by one reviewer that Cortese and colleagues found medications for ADHD to be less efficacious and less well tolerated in adults than in children; however, the application for methylphenidate to go on the WHO list was for children, adolescents and adults. The same reviewer declares that the application has not given any age restriction and that Cortese and colleagues conclude that 'Amphetamine is shown as preferred choice over methylphenidate and other medicines in adult',[8] which does not align with the application being for including methylphenidate as an essential medicine for adults as well.[7] Assessment of the overall benefit-to-risk ratio of methylphenidate is summarised by the reviewers as having low quality of evidence and being uncertain, given the lack of data after 12 weeks, the lack of data in children younger than 5 years, adverse effects of concern and the fact that the first-line treatment for ADHD is non-pharmacological. None of the reviewers recommends that methylphenidate is included on the WHO core list of essential medicines.

Letters of support

The application included an appendix, which contained 47 letters of support for the application that the WHO list should include methylphenidate. As some of the letters were cosigned by more than one person, 59 individuals, who primarily represented municipal and regional organisations for ADHD and ADHD family alliance organisations, signed the 47 support letters. A few, however, were from continental organisations. One such was a support letter from the umbrella organisation ADHD Europe, which was cosigned by national ADHD organisations from nine European countries. The remaining support letters were from individual practitioners from hospitals and clinics specialising in psychiatry or paediatrics. Seventeen of the letters were from Spanish ADHD organisations. A small handful of the letters were written in free form; however, most letters appeared derived from a premade generic template, which had been given to the organisations for them to insert their name and country. We base this on the fact that almost all of the support letters are identical and from an oversight in a letter when the organisation did not delete 'insert country' from the template.

Implications for evidence-based research and clinical practice

ADHD is considered a chronic condition,[18] and children, adolescents and adults are treated for many years. It is the second time that WHO rejects to include methylphenidate on their core list of essential medicines due to uncertainties in the estimates of benefits and harms. Hereby, WHO has now clearly stated that there is uncertain evidence on group level to support the claim that methylphenidate is beneficial in treating children, adolescents and adults with ADHD. Future randomised clinical trials should be at low risks of bias with the necessary sample size and of longer duration and follow-up time.[6 14 15]

Many clinicians and researchers find that methylphenidate gives symptom reduction in some children, adolescents and adults with ADHD, but the sizes of these groups are unclear. Systematic reviews should include individual participant data, which would allow us to assess intervention effects across modifiers, like ADHD subtypes, comorbidities and dose.[15] Such data should be available for both short-term and long-term effects.[6 14 15] Using this type of meta-analysis, we might discover the subgroups of patients with ADHD that will benefit the most from methylphenidate, as well as those that benefit the least. It is also important to secure blinding (use of an 'active' placebo control group) as the participants in the medication groups could have been subject to systematic unblinding, because of the well-known adverse events of methylphenidate compared with placebo interventions.[6 9 14 15]

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