WHO Essential Medicines List and methylphenidate for ADHD in children and adolescents

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In 2019, and again in 2021, the WHO Expert Committee on the selection and use of essential medicines declined to grant methylphenidate the status of an essential medicine. This decision was made after a thorough examination using a commonly accepted and consensus-based procedure, which concluded that "evidence for efficacy is inconclusive, with a high risk of bias or unclear data in a substantial proportion of studies; lack of data beyond 12 weeks; lack of data in children under 5 years old; concerning adverse effects; non-pharmacological interventions are the first-line therapy for ADHD."[1]

A Comment by Samuele Cortese and colleagues pleads for this decision to be rethought, and argues that methylphenidate has a proven track record of efficacy and safety.[2] Cortese and colleagues criticise a comprehensive Cochrane review,[3] which concluded that all the trials included were of poor quality, that unmasking was probably common, and that there was little evidence on long-term outcomes, and therefore the review authors could not conclude that methylphenidate would improve the lives of children and adolescents with ADHD. A 2023 update of the review came to the same conclusions,[4] as do other Cochrane reviews.

The trials presented by Cortese and colleagues are short-term,[2] but patients are usually treated for several years. Trials with long-term follow up, such as the Multimodal Treatment of ADHD trial, have not found any positive long-term effects of methylphenidate on ADHD behaviours, academic performance, or the risks of delinquency, addiction, depression, anxiety, or impairment.[5,6] Other studies found that when there are differences in long-term outcome, children on stimulants (such as methylphenidate) often have worse outcomes than those not taking them, regardless of initial severity, with physical (eg, blood pressure), psychiatric (eg, mood disorders), and academic problems found to be more common in patients on long-term medication.[7,8]

Cortese and colleagues claim that, "individuals with ADHD have significantly fewer unintentional physical injuries, motor vehicle accidents, substance use disorders, and criminal acts, and have an improvement in academic functioning during periods when they are taking methylphenidate, compared with periods when they are not taking methylphenidate."[2] The studies Cortese and colleagues quote use individuals as their own controls; however such studies cannot account for withdrawal reactions, the reasons for disengagement from treatment (such as other psychiatric conditions or life stressors), or if participants were actually taking medication at the time of the event.

Methylphenidate is an amphetamine analogue, and therefore a potentially addictive controlled substance. As a CNS stimulant, methylphenidate increases parameters such as blood pressure, body temperature, and heart rate. People using amphetamines and their analogues generally want less sleep, have less appetite, and, according to the US Food and Drug Administration package insert, are at increased risk of serious health consequences, such as sudden death, heart attack, or stroke. It is not known whether amphetamines and their analogues hamper brain development, but it is known that methylphenidate reduces growth in children.[9] Increasing circulation of a potentially addictive substance in any society means that it has so-called street value, and can expose people with or without a diagnosis of ADHD to unnecessary harms—emergency room visits linked to misuse of methylphenidate have been rising in the USA.[10]

From our perspective, the decision on methylphenidate by the WHO expert committee aligns with the latest WHO guidelines and international scientific literature. WHO now rightly advocates for expanding the horizons of practice, research, and public policy beyond the biomedical model, in favour of psychosocial interventions and a more person-centred rights-based approach that holistically considers all life contexts.

We declare no competing interests.

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1 WHO. A.21 Methylphenidate—attention-deficit hyperactivity disorder—EML and EMLc. 2023. https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/23rd-expert-committee/a21-methylphenidate (accessed Nov 1, 2023).
2 Cortese S, Coghill D, Mattingly GW, Rohde LA, Wong ICK, Faraone SV. WHO Model Lists of Essential Medicines: methylphenidate for ADHD in children and adolescents. *Lancet Psychiatry* 2023; **10:** 743–44.
3 Storebø OJ, Krogh HB, Ramstad E, et al. Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials. *BMJ* 2015; **351:** h5203.
4 Storebø OJ, Storm MRO, Pereira Ribeiro J, et al. Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). *Cochrane Database Syst Rev* 2023; **3:** CD009885.
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For more on the **US Food and Drug Administration package insert** for methylphenidate see https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/010187s071s082,018029s041s051lbl.pdf

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10 Shearer RD, Jones A, Howell BA, Segel JE, Winkelman TNA. Associations between prescription and illicit stimulant and opioid use in the US, 2015–2020. *J Subst Abuse Treat* 2022; **143:** 108894.

In a Comment from Samuele Cortese and colleagues[1] on the Review by Papola and colleagues that describes the 2023 changes to the WHO Model List of Essential Medicines (EML),[2] Cortese and colleagues focus on the EML committee's decisions not to support the inclusion of methylphenidate as an essential medicine for the treatment of ADHD in children and adolescents. Two applications were made to WHO, one in 2018 and one in 2020, to include methylphenidate in the EML. Both applications were rejected by the EML committee due to uncertainty about the quality of the evidence and the benefit to harm balance of methylphenidate over long-term use (ie, 52 weeks and beyond). Cortese and colleagues state that the first decision by WHO in 2018 to not add methylphenidate to the EML was largely based on our Cochrane review published in 2015.[3] It is a bit disheartening to observe our work being referenced in a manner that does not accurately reflect the content of our review,[3] the findings of which were supported by our 2023 update.[4] Moreover, the risks of adverse events[5] are discounted by Cortese and colleagues by reference only to recent observational evidence (rather than a more comprehensive assessment of harms in observational studies and randomised clinical trials).[1]

To accept a long-term pharmacological treatment for children when there is no strong evidence of effects is problematic.[3,4,5,6]

The latest EML for children was released by WHO on July 26, 2023.[7] In the context of mental disorders, changes to the EML for children involved the eradication of the substances chlorpromazine, haloperidol, and fluoxetine. With these alternations, the current EML contains no medications of any kind to treat mental disorders in children younger than 12 years, which aligns with current evidence.[8,9]

WHO sends an important signal regarding the evidence required for medications to be accepted in the EML.[7] WHO indicates that precautions are warranted regarding any pharmacological treatment of mental disorders for children younger than 12 years. From an evidence-based perspective, we believe the precautions to be an ethical and sound stance.

WHO emphasises that decision makers in national health-care systems should seize the revision of the EML mental health section as an opportunity to take actions that improve the evidence base of both pharmacological and psychosocial interventions. Now, more than ever, mental health treatments should be firmly placed on health-policy agendas worldwide, and these treaments should be based on solid evidence.

JPR, OJS, and CG have been co-authors of a Cochrane systematic review on methylphenidate for children with ADHD. All other authors declare no competing interests.

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1 Cortese S, Coghill D, Mattingly GW, Rohde LA, Wong ICK, Faraone SV. WHO Model Lists of Essential Medicines: methylphenidate for ADHD in children and adolescents. *Lancet Psychiatry* 2023; **10:** 743–44.

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Authors' reply

Sébastien Ponnou and colleagues and Ole Jakob Storebø and colleagues expressed concerns around our plea for methylphenidate to be included in the