**AACAP endorses the inclusion of methylphenidate in the WHO Model lists of essential medicines**

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**Conflicts of interest**

SC declares honoraria from the British Association of Psychopharmacology, Canadian ADHD Resource Alliance, Association for Child and Adolescent Mental Health, and Medice. He has served on the advisory board of the Association

for Child and Adolescent Mental Health (ACAMH). He has served as deputy editor of Evidence Based Mental Health (now BMJ Mental Health), associate editor of Child and Adolescent Mental Health, and on the editorial board of the Journal of Child Psychology and Psychiatry. He declares grants form the NIHR and European Research Agency.

DC declares grants from the National Health and Medical Research Council and the Medical Research and Futures Fund; royalties from Oxford University Press and Cambridge University Press; honoraria from Takeda, Medice, Servier, and Novartis; support for attending meetings or travel from the European College of Neuropsychopharmacology; and is the Director of the Australian ADHA Professionals Association and the European Network for Hyperkinetic Disorders.

GWM declares consulting fees, honoraria, and participation data safety monitoring board for Corium, Supernus, Ironshore, Tris, Akilly, Lumos Lab, and Revibe; and stock in Revibe.

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The World Health Organization (WHO) essential medicines list (EML) includes a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe, and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

Despite decades of clinical use, the WHO continues to exclude methylphenidate for Attention-Deficit/Hyperactivity Disorder (ADHD) from its EML.1 The exclusion of methylphenidate has dire implications for millions of individuals with ADHD worldwide, especially those living in Low and Low-Middle Income Countries (LMIC), where governmental decisions to make medicines available are contingent on EML listing.

A committee updates the EML every two years. Applications to include or exclude medications from the list by institutions outside the WHO are permitted. Two successive applications (2019 and 2021), requesting the addition of methylphenidate to the EML, were rejected. For the first application, the committee deemed the evidence from randomized controlled trials (RCTs) to be of uncertain quality, reflecting the conclusions of a Cochrane standard (pairwise) meta-analysis.2 That meta-analysis has been criticized for using an idiosyncratic approach to assess the quality of the evidence.3 Indeed,96.8% of the trials included in this meta-analysis were rated by the review team to be at high risk of bias. Notably, the authors added an item about vested interest to the standard Cochrane tool for assessing the risk of bias. This item downgraded the level of evidence of trials funded by parties that might have had a conflict of interest (e.g., a manufacturer of methylphenidate) or where trial authors reported potential conflicts of interest. It is unclear how this criterion was operationalised (e.g., what number of authors with supposed conflict triggered a downgrade?).

The second application presented a broader evidence base, with findings from RCTs summarised using a comprehensive and up-to-date network meta-analysis (NMA), 4 an approach that provides more precise estimates than standard (pairwise) meta-analyses. This NMA showed a high effect size for methylphenidate in terms of efficacy (standardized mean difference, according to clinicians’ ratings: 0.78, 95% CI: 0.62-0.93), with the evidence rated as being of moderate quality according to the gold standard tool (GRADE). Importantly, this NMA reduced the proportion of unclear items in the risk of bias tool from 63.5% to 35.2% by gathering additional unpublished information. This suggests that previous estimates of “unclear evidence” reflect mostly poor reporting rather than poor quality of the RCTs per se.

Crucially, the second application also included a large body of evidence from large real-world self-controlled studies, which address several of the well know limitations of RCTs such as the inclusion of participants that are not representative of patients seen in “real world” clinical practice. Evidence from these real world studies demonstrates that, during periods when they are taking methylphenidate, individuals with ADHD have significantly less unintentional physical injuries, motor vehicle accidents, substance use disorders, and criminal acts, and improved academic functioning, compared to periods when they are off medication.5 Despite this compelling evidence, the WHO once again rejected the application, requesting evidence from an RCT of at least 52 weeks to prove the long-term effectiveness and safety. This requirement is puzzling, considering, for instance, that the longest trial including fluoxetine - which is listed in the EML for adults- retained in a comprehensive NMA of RCTs in adults, was of 24 weeks (average: 8.2 weeks).6 Of note, data from withdrawal RCTs show the persistence of clinically meaningful benefits with continued long-term treatment, for instance after more than 4 years of treatment in the study by Matthijssen et al.7.

Furthermore, since the second rejection by the Committee, additional evidence, including a 2-year, naturalistic, longitudinal, controlled study,8 has confirmed that long-term treatment with methylphenidate is safe.

This puzzling situation around the exclusion of methylphenidate from the EML was highlighted in a recent Correspondence published in The Lancet Psychiatry.9 This was endorsed by 16 professional associations /groups of representatives of people with lived experience. We were pleased that the American Academy of Child and Adolescent Psychiatry (AACAP) was one of these associations, in line with a previous endorsement of the second WHO application that the then AACAP President, Dr Gabrielle Carlson, signed in 2020 (https://cdn.who.int/media/docs/default-source/essential-medicines/2021-eml-expert-committee/public-comments/a21\_methylphenidate\_aacap.pdf?sfvrsn=66b28049\_6).

With AACAP and the other associations, alongside the millions of professionals and people with lived experience they represent, we look forward to a more balanced and comprehensive assessment of the evidence on the efficacy/effectiveness and safety of methylphenidate for ADHD.

**References**

1. Purgato M, Barbui C. What is the WHO essential medicines list? Epidemiol Psychiatr Sci 2012;21:343-5. doi: 10.1017/S204579601200039X

2. 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. doi: 10.1002/14651858.CD009885.pub3.

3. Banaschewski T, Buitelaar J, Chui CS, et al. Methylphenidate for ADHD in children and adolescents: throwing the baby out with the bathwater. Evid Based Ment Health 2016;19:97-9. doi: 10.1136/eb-2016-102461

4. Cortese S, Adamo N, Del Giovane C, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. Lancet Psychiatry 2018;5:727-38. doi: 10.1016/S2215-0366(18)30269-4.

5. Chang Z, Ghirardi L, Quinn PD, Asherson P, D'Onofrio BM, Larsson H. Risks and Benefits of Attention-Deficit/Hyperactivity Disorder Medication on Behavioral and Neuropsychiatric Outcomes: A Qualitative Review of Pharmacoepidemiology Studies Using Linked Prescription Databases. Biol Psychiatry 2019;86:335-43. doi: 10.1016/j.biopsych.2019.04.009.

6. 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.

7. Matthijssen AM, Dietrich A, Bierens M, et al.. Continued Benefits of

Methylphenidate in ADHD After 2 Years in Clinical Practice: A Randomized

Placebo-Controlled Discontinuation Study. Am J Psychiatry. 2019 ;

1;176(9):754-762. doi: 10.1176/appi.ajp.2019.18111296.

Lancet. 2018; 7;391(10128):1357-1366. doi: 10.1016/S0140-6736(17)32802-7.

8. Man KKC, Häge A, Banaschewski T, et al. Long-term safety of methylphenidate in children and adolescents with ADHD: 2-year outcomes of the Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects (ADDUCE) study. Lancet Psychiatry 2023;10:323-33. doi: 10.1016/S2215-0366(23)00042-1.

9. Cortese S, Coghill D, Mattingly GW, et al. WHO Model Lists of Essential Medicines: methylphenidate for ADHD in children and adolescents. Lancet Psychiatry 2023;10:743-4. doi: 10.1016/S2215-0366(23)00292-4.