EUNETHYDIS

2025-04-18

To the: emlsecretariat@who.int

WHO Expert Committee on Selection and Use of Essential Medicines

RE: Application reference: A.19 Methylphenidate – attention deficit hyperactivity disorder

Dear Members of the Essential Medicines for Children Committee,

The purpose of this letter is to strongly support the inclusion of methylphenidate in the WHO Model List of Essential Medicines for the treatment of children and adolescents between the ages of 6 and 17 years with Attention-Deficit/Hyperactivity Disorder (ADHD), as well as for the corresponding application "A.19 Methylphenidate – attention deficit hyperactivity disorder."

Essential medicines are those that satisfy the priority health care needs of a population. They are selected with due regard to disease prevalence and public health relevance, evidence of efficacy and safety and comparative cost-effectiveness. They are intended to be available in functioning health systems at all times, in appropriate dosage forms, of assured quality and at prices individuals and health systems can afford.

Methylphenidate, which has been used as a first line treatment for ADHD in children and adolescents for more than 40 years in many countries[1], meets all criteria listed above for inclusion in the list. To summarize this shortly:

1. ADHD is a common neurodevelopmental condition with an estimated world-wide prevalence of 5% to 7% in children and adolescents[2], with over 50% of them benefiting from methylphenidate[3] [4]. Although most studies are from North America and Europe, ADHD has been recognised and studied across all continents, including South America, Africa, Asia, Middle East, and Oceania[5]. It is associated with substantive burden for the affected children, their families and society. These include increased risk for poor academic and school performance, school drop-out, unemployment, poor physical health, initiation of smoking and substance use/misuse, and co-occurrence of oppositional and antisocial behaviour, suicidality and mood/anxiety problems[6].
2. There is abundant evidence that methylphenidate is effective in lowering symptom severity[7], reducing risk for negative adverse consequences and complications (i.e., protecting against substance use, suicidality, school drop-out, and later mood disorder/anxiety[8]). Placebo-controlled discontinuation studies have demonstrated long-term efficacy over a period of at least 2 years[9].
3. There is clear evidence that methylphenidate is significantly more effective than a whole variety of non-pharmacological interventions, such as behaviour therapy, diet and lifestyle interventions, and neurofeedback[10].
4. There is clear evidence that methylphenidate treatment is safe, without alarming and life-threatening short and long term side effects and has good tolerability[11].
5. Given the above, methylphenidate medication is a recommended treatment option in all authoritative international guidelines for ADHD, such as those by NICE (UK), SIGN (Scotland), CADDRA (Canada), AACAP (USA), AADPA (Australia), and by guidelines in many other countries including Germany, Hungary, India, Brazil, Japan, Netherlands, and the Scandinavian countries.

We write this letter on behalf of the European Network for ADHD (EUNETHYDIS)[1] and the European ADHD Guidelines Group (EAGG). EUNETHYDIS is a network of 130 experts in ADHD, founded about 40 years ago that aims to facilitate high-quality research on ADHD and its broader societal impact through collaboration between clinical and basic science researchers across Europe in the spirit of openness, trust, and support. While the network is based in Europe, it embraces a global perspective. Over the past four decades, EUNETHYDIS has been instrumental in supporting research studies on the treatment of ADHD, including pharmacological interventions.

In 2010, EUNETHYDIS formally established the European ADHD Guidelines Group (EAGG)[2], a group of 29 clinicians and researchers aimed at rigorously appraising the literature and providing evidence-based guidance for daily clinical questions in ADHD practice. The EAGG published a landmark network meta-analysis of 133 randomized controlled trials of ADHD medications, showing a high effect size (around 0.80) on ADHD core symptom severity and similar tolerability to placebo for methylphenidate[7]. Both pharmaceutical company–sponsored and non–pharmaceutical company–sponsored RCTs [such as the MTA study[12] or a large (N ~ 500) Canadian RCT[13]] show beneficial effects of methylphenidate and generally good tolerability.
Notably, the EAGG has also conducted a series of meta-analyses on non-pharmacological interventions, including behavioural interventions, cognitive training, neurofeedback, and dietary interventions, showing that their value in treating the core symptoms of ADHD remains uncertain[14-17], although they may be beneficial for important comorbid conditions (e.g., oppositional defiant disorder, in the case of behavioral interventions[18]).

EUNETHYDIS has also been closely involved in the development and delivery of the Attention-Deficit Hyperactivity Disorder Drugs Use Chronic Effects (ADDUCE) consortium[3]. This network of 16 universities across Europe, funded by the European Research Agency, conducted the largest naturalistic controlled study worldwide to investigate the safety of methylphenidate over a two-year period. The ADDUCE study[19] showed that long-term treatment with methylphenidate is safe, with no evidence to support the hypothesis that it leads to reductions in growth. Although methylphenidate-related pulse and blood pressure changes were relatively small, they require regular monitoring, as per current guidelines and good clinical practice.

We understand that, while most researchers and clinicians in the field acknowledge the benefits of methylphenidate and its overall good tolerability, a minority is concerned around quality of evidence of randomised controlled trials and the lack of randomised controlled trials in the longer term (after 1 year). The assessment of quality of evidence is based on tools involving subjective decisions which may introduce bias (including ideological bias). In our network meta-analysis [7], the overall quality of the evidence using the rigorous GRADE framework and adopting a conservative approach was deemed as moderate - high in 5 domains and moderate in 1 domain. Regarding the supposed lack of long-term evidence, while it is unethical to conduct long-term randomised trials when methylphenidate has already been shown to be superior to other treatments, we would like to emphasize that trials using the discontinuation design demonstrate the persistence of methylphenidate's benefits over time[9 20].

While some critics have tended to focus solely on evidence from randomised controlled clinical trials, we believe that this narrow focus is unwarranted, especially given the poor representativeness of trial participants. Indeed, there is evidence that around 50% of individuals with ADHD would not be recruited for clinical trials[21]. In contrast, evidence from studies designed to provide insights into cause-and-effect relationships has shown remarkable overall benefits of methylphenidate. Studies using the within individual design have demonstrated reductions in physical injuries, motor vehicle accidents,

[1] https://eunethydis.eu/
[2] https://eunethydis.eu/eunethydis-initiatives/european-adhd-guideline-group/
[3] https://cordis.europa.eu/project/id/260576/reporting

depression, and criminal acts, as well as improvements in academic function[8]. Rigorous evidence from target trial emulation design shows a reduction in mortality with stimulant (including methylphenidate) treatment[22].

Methylphenidate is only one component of the multimodal management of individuals with ADHD, which must include non-pharmacological approaches as well. Some individuals may not benefit from or tolerate methylphenidate, but most individuals with ADHD will benefit from and tolerate it well. This is in line with the views expressed by many individuals with lived experience of ADHD, who have collaborated/interacted with EUNETHYDIS over the years.

In conclusion, we deem that many countries around the world - including low- and middle-income countries, where the prevalence of ADHD (when rigorously assessed) has been shown to be similar to that in so-called developed countries[2] - will benefit from the inclusion of methylphenidate in the EML.

Sincerely,

Professor Samuele Cortese, MD, PhD

Chair EAGG

Professor Jan Buitelaar, MD, PhD

Co-Chair EAGG

Professor Sven Bölte, PhD

Co-Chair of EUNETHYDIS

References

1. Cortese S. Pharmacologic Treatment of Attention Deficit-Hyperactivity Disorder. *N Engl J Med* 2020;383(11):1050-56. doi: 10.1056/NEJMra1917069
2. Ayano G, Demelash S, Gizachew Y, et al. The global prevalence of attention deficit hyperactivity disorder in children and adolescents: An umbrella review of meta-analyses. *J Affect Disord* 2023;339:860-66. doi: 10.1016/j.jad.2023.07.071 [published Online First: 20230724]
3. Coghill DR, Newcorn JH, Chen J, et al. Post hoc analyses of response rates to pharmacological treatments in children and adolescents with attention-deficit/hyperactivity disorder. *J Psychopharmacol* 2020;34(8):874-82. doi: 10.1177/0269881120904949 [published Online First: 20200211]
4. Su Y, Li H, Chen Y, et al. Remission Rate and Functional Outcomes During a 6-Month Treatment With Osmotic-Release Oral-System Methylphenidate in Children With Attention-Deficit/Hyperactivity Disorder. *J Clin Psychopharmacol* 2015;35(5):525-34. doi: 10.1097/jcp.0000000000000389
5. Polanczyk G, de Lima MS, Horta BL, et al. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *Am J Psychiatry* 2007;164(6):942-8. doi: 10.1176/ajp.2007.164.6.942
6. Faraone SV, Asherson P, Banaschewski T, et al. Attention-deficit/hyperactivity disorder. *Nat Rev Dis Primers* 2015;1:15020. doi: 10.1038/nrdp.2015.20 [published Online First: 20150806]
7. 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(9):727-38. doi: 10.1016/s2215-0366(18)30269-4 [published Online First: 20180807]
8. Chang Z, Ghirardi L, Quinn PD, et al. 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(5):335-43. doi: 10.1016/j.biopsych.2019.04.009 [published Online First: 20190417]
9. 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;176(9):754-62. doi: 10.1176/appi.ajp.2019.18111296 [published Online First: 20190521]
10. Catalá-López F, Hutton B, Núñez-Beltrán A, et al. The pharmacological and non-pharmacological treatment of attention deficit hyperactivity disorder in children and adolescents: A systematic review with network meta-analyses of randomised trials. *PLoS One* 2017;12(7):e0180355. doi: 10.1371/journal.pone.0180355 [published Online First: 20170712]
11. Cortese S, Holtmann M, Banaschewski T, et al. Practitioner review: current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. *J Child Psychol Psychiatry* 2013;54(3):227-46. doi: 10.1111/jcpp.12036 [published Online First: 20130107]
12. MTA group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The MTA Cooperative Group. Multimodal Treatment Study of Children with ADHD. *Arch Gen Psychiatry* 1999;56(12):1073-86. doi: 10.1001/archpsyc.56.12.1073
13. Grizenko N, Qi Zhang DD, Polotskaia A, Joober R. Efficacy of Methylphenidate in ADHD Children across the Normal and the Gifted Intellectual Spectrum. *J Can Acad Child Adolesc Psychiatry* 2012;21(4):282-8.
14. Sonuga-Barke EJ, Brandeis D, Cortese S, et al. Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. *Am J Psychiatry* 2013;170(3):275-89. doi: 10.1176/appi.ajp.2012.12070991

15. Westwood SJ, Aggensteiner PM, Kaiser A, et al. Neurofeedback for Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-Analysis. *JAMA Psychiatry* 2025;82(2):118-29. doi: 10.1001/jamapsychiatry.2024.3702
16. Westwood SJ, Conti AA, Tang W, et al. Clinical and cognitive effects of external trigeminal nerve stimulation (eTNS) in neurological and psychiatric disorders: a systematic review and meta-analysis. *Mol Psychiatry* 2023;28(10):4025-43. doi: 10.1038/s41380-023-02227-4 [published Online First: 20230906]
17. Stevenson J, Buitelaar J, Cortese S, et al. Research review: the role of diet in the treatment of attention-deficit/hyperactivity disorder--an appraisal of the evidence on efficacy and recommendations on the design of future studies. *J Child Psychol Psychiatry* 2014;55(5):416-27. doi: 10.1111/jcpp.12215 [published Online First: 20140219]
18. Daley D, van der Oord S, Ferrin M, et al. Behavioral interventions in attention-deficit/hyperactivity disorder: a meta-analysis of randomized controlled trials across multiple outcome domains. *J Am Acad Child Adolesc Psychiatry* 2014;53(8):835-47, 47.e1-5. doi: 10.1016/j.jaac.2014.05.013 [published Online First: 20140626]
19. 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(5):323-33. doi: 10.1016/s2215-0366(23)00042-1 [published Online First: 20230320]
20. Buitelaar JK, Trott GE, Hofecker M, et al. Long-term efficacy and safety outcomes with OROS-MPH in adults with ADHD. *Int J Neuropsychopharmacol* 2012;15(1):1-13. doi: 10.1017/s1461145711001131 [published Online First: 20110729]
21. Garcia-Argibay M, Chang Z, Brikell I, et al. Evaluating ADHD medication trial representativeness: a Swedish population-based study comparing hypothetically trial-eligible and trial-ineligible individuals. *Lancet Psychiatry* 2025;12(2):131-39. doi: 10.1016/s2215-0366(24)00396-1 [published Online First: 20250106]
22. Li L, Zhu N, Zhang L, et al. ADHD Pharmacotherapy and Mortality in Individuals With ADHD. *JAMA* 2024;331(10):850-60. doi: 10.1001/jama.2024.0851