PROPOSAL FOR THE INCLUSION OF METHYLPHENIDATE ON THE WHO MODEL LIST OF ESSENTIAL MEDICINES FOR THE TREATMENT OF CHILDREN AND ADOLESCENTS AGED 6-17 YEARS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

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SECTION 1: SUMMARY STATEMENT OF THE PROPOSAL

This application proposes the addition of methylphenidate to the list of the EMLc and EML for the treatment of children and adolescents between the ages of 6 to 17 years with attention-deficit/hyperactivity disorder (ADHD).

ADHD is one of the most common mental disorders in children and young people and the 39th leading cause of years lived with disability among those aged 5 to 14 years. The diagnosis is associated with poorer quality of life, worse educational attainment, and higher risk of unintentional injuries and death in childhood and adolescence.

In support of this application, we review the best available evidence on the efficacy, effectiveness, and safety of methylphenidate as compared to placebo/no treatment for children and adolescents aged 6 to 17 years with ADHD as there are no other alternative medicines currently included on the EMLc or EML for this indication.

We consider several important issues raised by the Expert Committee with regards to the two previous applications made by other independent groups. Specifically, there was a request for evidence acquired over long periods of time, ideally more than 52 weeks given that ADHD can be a chronic condition, requiring long-term management. The pertinent available evidence is presented in this application as we consider in depth the findings of two randomized controlled trials, both over 52 weeks duration, showing benefits in symptom reduction of moderate effect sizes, and randomized discontinuation trials that more indirectly point to sustained long-term benefits at least after 2 years of treatment with methylphenidate. We review evidence of adverse events, particularly those tied to long-term treatment. We find no evidence of an increased risk of serious adverse events, including serious cardiovascular events in association with methylphenidate treatment. However, there was evidence of increased non-serious adverse events, particularly in some cardiovascular outcomes, with more mixed evidence regarding effects on height and weight. These adverse events underscore the need for monitoring throughout treatment.

Secondly, we note that the 2023 mhGAP guideline for treatment of ADHD recommends that methylphenidate should be a treatment option for those with ADHD in the context of a management plan that addresses psychosocial risks and vulnerabilities and environmental factors that have an impact on symptoms and functioning. This application would help allow this recommendation to be realized across low-middle income countries (LMICs).

Thirdly, we consider the feasibility of health care systems to provide the diagnostic and monitoring processes required for methylphenidate prescription. We note the growing integration of psychiatry into primary health care, with international increases in supervision and training by specialists of those in primary care settings which will support the scaling up of the management of ADHD, including the prescription and monitoring of methylphenidate.

The committee also raised concerns about the rating, by those conducting the Cochrane review of randomized controlled trials (RCTs), of the short-term effects of methylphenidate treatment as being of very low quality according to the Grading of Recommendations, Assessment,

Development and Evaluation (GRADE) approach. In this application, we provide a rationale for re-considering the evidence to be of at least moderate quality, both for its benefits and for its adverse events.

We respond to concerns raised in previous reviews about accuracy of the estimates of ADHD prevalence with reference to recent studies, including the Global Burden of Diseases 2021 survey, which estimated a global prevalence of ~1.95% for those aged 20 years or younger. Even in countries with the lowest estimated prevalence, there are thus millions of children and adolescents affected by the disorder.

Finally, to address important concerns about non-medical use of stimulants and diversion, we review recent estimates of the prevalence of such misuse/diversion, the potential harms, and pathways toward minimizing risk of misuse and diversion of these medicines.

SECTION 2: CONSULTATION WITH WHO TECHNICAL DEPARTMENTS

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Drs. Cataldi and Servilli are technical officers with the Brain Health Unit, Department of Mental Health and Substance Use, World Health Organization, Geneva, Switzerland.

We met with Drs. Cataldi and Servilli on the 3rd of July 2024 and then Dr. Cataldi on the 12th of August 2024. We have exchanged emails throughout the period until submission with Dr. Cataldi. He also reviewed this application and supports submission.

SECTION 3: OTHER ORGANIZATION(S) CONSULTED AND/OR SUPPORTING THE SUBMISSION

There were no organizations consulted for this application. Interested parties will be invited to provide comments on the submission during the public consultation phase on the WHO website.

SECTION 4: KEY INFORMATION SUMMARY FOR THE PROPOSED MEDICINE.

INN	Methylphenidate		
ATC Code	N06BA04		
Indication	Treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents aged 6-17 years		
ICD-11 code	6A05		
Dosage form	**Strength**	**EML**	**EMLc**
Tablet	5, 10, 20 mg	Yes	Yes
Extended-release capsule	10 to 60 mg	Yes	Yes
Extended-release tablet	18, 27, 36, 54, 72 mg	Yes	Yes

SECTION 5: LISTING AS AN INDIVIDUAL MEDICINE OR REPRESENTATIVE OF A PHARMACOLOGICAL CLASS / THERAPEUTIC GROUP.

This proposal requests that methylphenidate be listed as an individual medicine. Among medicines used for the treatment of ADHD in children and adolescents, methylphenidate has the most comprehensive evidence of efficacy, effectiveness, safety, and cost-effectiveness.

SECTION 6: INFORMATION SUPPORTING THE PUBLIC HEALTH RELEVANCE.

The application proposes the inclusion of methylphenidate for the treatment of ADHD in children and adolescents (between ages 6-17 years). Below, we provide information and evidence supporting the public relevance of the proposed medicine for this indication and target population.

6.1 Diagnosis

6.1.1 Criteria

As formulated in the International Classification of Diseases 11th revision (ICD-11) *(1)*, ADHD is a neurodevelopmental disorder characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity that is outside the limits of normal variation expected for age and level of intellectual development and has direct negative impact on academic, occupational, or social functioning.

Inattention refers to difficulties in sustaining attention to tasks that do not provide a high level of stimulation or frequent rewards, distractibility, and problems with organization.

Hyperactivity refers to excessive motor activity and difficulties with remaining still, most impairing in structured situations that require behavioral self-control.

Impulsivity is a tendency to act in response to immediate stimuli without deliberation or consideration of the risks and consequences.

For the diagnosis of ADHD to be made, manifestations of inattention and/or hyperactivity-impulsivity must onset prior to age 12, last for at least 6 months, and cause impairment across situations and settings (e.g., home, school, work, with friends or relatives). Lastly, symptoms must not be better explained by another mental, behavioral, or neurodevelopmental disorder and must not be due to the effect of a substance or medication.

6.1.2 Diagnostic procedures

The diagnosis of ADHD can only be made by licensed professionals with training and expertise in the diagnosis of ADHD on the basis of a full clinical and psychosocial assessment of behaviors and symptoms in different settings of life; a developmental and psychiatric history; and assessment of mental state *(2)*. In the process of preparing ICD-11, the World Health Organization (WHO) provided diagnostic guidelines *(3)*, which have proved useful in lower resource settings, such as in LMICs *(4, 5)*. ADHD cannot be diagnosed through the use of questionnaires (including rating scales) alone, neuropsychological tests, or any other biomarkers (for instance, methods for imaging the brain or characterizing genetic features).

6.1.3 Reliability

The diagnosis of ADHD is reliable when performed by trained professionals using well-defined criteria. For instance:

- In field trials for the DSM-5, the diagnosis of ADHD as formulated in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), had very good inter-rater reliability (kappa = 0.6-0.79) across four participating child/adolescent sites *(6, 7)*.
- In Mexico, a study of 25 psychiatrists who each received a 4-hour training session on the ICD-11 diagnostic criteria for child and adolescent mental health

conditions found that the diagnosis of ADHD showed good inter-rater reliability (kappa = 0.46) *(5)*.

6.1.4 Validity

Children and adolescents with a diagnosis of ADHD have been found to have poorer quality of life and greater risk of several negative outcomes across their development compared to those without ADHD, which provides evidence of concurrent and predictive validity for the diagnosis of ADHD. For instance:

- In a systematic review and meta-analysis of 8 studies including 854 children and adolescents with ADHD, ADHD was associated with *substantially poorer quality of life* considering either parent- (Hedge's g [95% confidence interval] -1.67 [-2.57 to -0.78]) or child-reported (-1.28 [-2.01 to -0.56]) measures *(8)*.
- In a population-based cohort study conducted in Denmark with data from 629,622 children, having a diagnosis of ADHD was associated with *worse educational attainment*, such as lower likelihood of taking the final examination after 9 years of compulsory school and lower mean grades achieved on the test *(9)*.
- A systematic review of longitudinal prospective cohort or case-control studies with a minimum follow-up of 2 years identified that individuals with ADHD prior to 18 years of age were more likely to be *fired* and to face *unemployment (10)*.
- In another population-based cohort study conducted in Denmark with 4,231 individuals who received a diagnosis of ADHD at the ages of 4 to 15 years, individuals with ADHD had been convicted almost twice as frequently compared to matched (on sex and birth year) individuals without ADHD during a follow-up period of 15 years, and this association with *criminality* remained statistically significant after adjustment for psychiatric comorbidity, parental ADHD, parental educational status, parental psychopathology, family composition, placements outside the home, parental death, socioeconomic status, and urbanicity *(11)*.
- In a systematic review and meta-analysis of 28 observational studies including 350,938 children with ADHD, there was evidence of an association between ADHD diagnosis and *unintentional physical injuries (12)*.
- In a study using the Danish national registers that followed up 1.92 million children born between 1981 and 2011, having a diagnosis of ADHD at the ages 6 to 17 years was associated with *increased mortality* that remained statistically significant after adjustment for age, calendar year, sex, parental history of psychiatric disorders, maternal and paternal age at time of delivery, parental educational status, and parental employment status *(13)*.

6.1.5 Diagnosis in the context of other psychiatric disorders

As determined in ICD-11, for the diagnosis of ADHD to be made it is important to rule out that the symptoms of inattention and/or hyperactivity-impulsivity would be better explained by another mental, behavioral, or neurodevelopmental disorder. However, that is not equivalent to stating that the diagnosis of ADHD cannot be made, or is less reliable, in the presence of another condition. For instance, a study including 40 children and adolescents with ADHD plus depression showed that 90% maintained their diagnosis of ADHD when the overlapping depression symptoms were subtracted, and the percentage of children with diagnosis was not significantly different from the percentage obtained when the original criteria were adopted *(14)*.

6.2 Epidemiology

6.2.1. Prevalence

Systematic reviews and meta-analyses pooled data from hundreds of surveys on ADHD prevalence in probabilistic samples of children and adolescents (≤ 18 years) from the general population across the world. Those studies, published in 2007 and 2012, indicated that the prevalence ratios of ADHD were around ~5% *(15, 16)*. While there was between-study variability in prevalence estimates, differences reflected methodological characteristics (such as the exact diagnostic criteria used, and the use of single versus multiple informants), rather than pointing to true prevalence variance. The relative stability of ADHD prevalence across nations was supported by a follow-up systematic review and meta-analysis of 135 studies that found no significant prevalence differences across nation (considering North America, South America, Europe, Africa, Asia, Middle East, and Oceania) or time, as reflected by the year of publication *(17)*.

More recently, the Global Burden of Diseases (GBD) 2021 survey, (https://vizhub.healthdata.org/gbd-results/) *(18)* estimated a prevalence of 1.95% (95% uncertainty intervals [UI] 1.34, 2.78) for those aged 20 years or younger. This estimate corresponds to 47 million children and young people (95% UI 32, 67 million) with ADHD.

For the GBD Study 2019, the investigators prepared a separate report for the global, regional, and national burden of 12 mental disorders, including ADHD, in 204 countries and territories *(19)*. This study found the highest prevalence estimates in the "High-Income" region (3.63%; 95% UI 2.4, 5.09) and areas of "High SDI" (3.5%; 95% UI 2.35, 4.93); and the lowest prevalence estimates in "Sub-Saharan Africa" (0.85%, 95% UI 0.5, 1.23) and areas of "Low SDI" (0.94%; 95% UI 0.63, 1.36). However, the extent to which these findings are true differences across regions is unclear, as data from some countries, in particular LMICs, are more likely to be imputed, as recently raised by independent researchers *(20)*. Indeed, in a re-analysis of the same dataset using more traditional meta-regression analyses, investigators were unable to find differences in the prevalence ratios between LMIC and high-income countries (5.65% versus 5.47%). Similarly, there was no significant association between SDI and prevalence ratios *(21)*. Nevertheless, GBD Study 2021 still estimated that almost 5 million individuals aged < 20 years lived with ADHD in "Sub-Saharan Africa" (4.89 million; 95% UI 3.27, 7.14) and areas of "Low SDI" (5.28 million; 95% UI 3.56, 7.68), reinforcing the public health importance of ADHD in children and adolescents. Other meta-analyses return higher prevalence estimates. For example, a recent meta-analysis of 59 studies in Middle Eastern and North African nations returned a pooled prevalence of ADHD in children and adolescents of 10.1% (95% CI 7 to 12), albeit with high heterogeneity across studies (I2 =99.86)*(22)*.

6.2.2 Burden

With regards to GBD Study 2021 estimates of burden, ADHD was the 39th (out of 302) leading cause of years of life lived with disability (YLDs) for children and adolescents aged 5 to 14 and 49th when also including adolescents between 15 to 20 years of age.

As mentioned above in *Section 6.1.4*, a diagnosis of childhood ADHD is also associated with poor quality of life, worse educational attainment, unemployment, criminality, increased risk of physical injuries, and higher mortality *(8-13)*.

Additionally, ADHD is also associated with substantial socioeconomic costs. A systematic review and meta-analysis published in 2024 pooled data from 32 studies from 2007 to 2023 that were identified across nine databases. Children with ADHD were associated with higher costs ($162-18,340) than their unaffected counterparts ($0-2,540) *(23)*.

6.3. Alternative medicines currently included on the Model Lists

Besides methylphenidate, the following medicines have been approved by regulatory agencies such as the US Food and Drug Administration (FDA), or the EU European Medicines Agency (EMA), for the treatment of children and adolescents (ages 5 to 17 years) with ADHD *(24)*:

- Dexmethylphenidate
- Amphetamines (e.g., mixed amphetamine salts, dextroamphetamine, lisdexamfetamine)
- Atomoxetine
- Guanfacine
- Clonidine
- Viloxazine

None of them are currently included on the Model Lists.

There are two medicines currently included on the Model Lists that may be used off-label for ADHD in children and adolescents: bupropion (first added in 2021 for nicotine dependence) and clomipramine (first added in 1993 for obsessive-compulsive disorder). However, these medicines are not proposed for addition to the EML for ADHD as the strength of the available evidence supporting the use of these medications for children and adolescents with ADHD is limited, being examined in relatively few placebo-controlled RCTs, considered below.

6.3.1 Bupropion

Only one double-blind, parallel arms, placebo-controlled study published in 1996 investigated the effects of bupropion (150-250 mg/d with a flexible titration) in 109 children aged 6-12 years old *(25)*. That study identified benefits of treatment compared to placebo with regards to ADHD symptoms based on both parent and teacher reports after 5 weeks of treatment.

6.3.2 Clomipramine

Only one double-blind, crossover arms, placebo-controlled study published in 1983 investigated the effects of clomipramine in 12 children aged 5.9 to 11.6 years *(26)*. That study indicated that clomipramine was not more efficacious than placebo in ameliorating global disturbing classroom behavior.

A systematic review and meta-analysis published by Cochrane identified six RCTs (five of desipramine, one of nortriptyline) with a total of 216 children and adolescents (ages 6 to 18 years) that tested a tricyclic antidepressant against placebo for ADHD *(27)*. While desipramine improved ADHD symptoms as assessed by parents (SMD -1.42; 95% confidence interval -1.99 to -0.85) and teachers (-0.97; -1.66 to -0.28), the evidence was considered of low quality. Additionally, there are concerns around the safety of desipramine for the cardiovascular system *(28, 29)*. Hence, the authors concluded that the evidence supporting the clinical use of desipramine for the treatment of children with ADHD was weak *(27)*.

SECTION 7: TREATMENT DETAILS.

Methylphenidate is delivered through different formulations (short-acting, intermediate, long-acting) that are currently available in the market. Below we highlight the formulations for which there is a generic drug authorized by the US FDA *(30)*. The data outlined below may be easily accessed and transparently verified in the Drugs @ FDA and the DailyMed websites (https://dailymed.nlm.nih.gov/dailymed/index.cfm; https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm).

7.1 Dosage regimen

For dosage regimens, data are taken from the FDA label of each formulation.

7.1.1 Methylphenidate hydrochloride (tablet; oral)

For children 6 years and older, the initial dose is 5 mg twice daily (before breakfast and lunch) with gradual increments of 5 to 10 mg weekly. Daily dosage above 60 mg is not recommended. If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, the drug is discontinued.

7.1.2 Methylphenidate hydrochloride (capsule, extended release; oral)

Methylphenidate hydrochloride extended-release capsule (LA) is for oral administration once daily in the morning. Capsules may be swallowed as whole capsules or alternatively may be administered by sprinkling the capsule contents onto a palatable substance (e.g., applesauce), for immediate consumption. Capsules and/or their contents should not be crushed, chewed, or divided.

The recommended starting dose of methylphenidate hydrochloride extended-release capsule (LA) is 20 mg once daily, but when in the judgment of the clinician a lower initial dose is appropriate, patients may begin treatment with 10 mg. Dosage may be adjusted in weekly 10 mg increments to a maximum of 60 mg/day taken once daily in the morning, depending on tolerability and degree of efficacy observed. Daily dosage above 60 mg is not recommended.

7.1.3 Methylphenidate hydrochloride (tablet, extended release; oral)

Methylphenidate hydrochloride extended-release tablets should be taken once daily in the morning and swallowed whole with liquids. Tablets should not be chewed or crushed and may be taken with or without food.

For children 6 years of age or older and adolescents new to methylphenidate, the recommended starting dosage is 18 mg once daily. Dosage may be increased by 18 mg/day at weekly intervals and should not exceed 54 mg/day in children and 72 mg/day in adolescents.

For patients currently using methylphenidate, dosing is based on current dose regimen and clinical judgment.

7.2 Duration of treatment

ADHD is a chronic condition that shows variable courses over development *(31)*. A systematic review of observational studies published in 2016 reported a persistence of the diagnosis across childhood and adolescence into early adulthood in around 50% *(31)*. More recent studies find similar rates of persistence, but also emphasize that for many children and adolescents the

symptoms of ADHD can wax and wane with age, leading to periods of remission and recurrence *(32, 33)*. Thus, it is important for the child or young person to have repeated assessments over time to assess the need for continued treatment with methylphenidate, as stated in the mhGAP guidelines. This approach also represents current best practice endorsed by other critically appraised guidelines such as the National Institute for Health & Care Excellence (NICE) *(2)*.

Considering the evidence base from RCTs comparing methylphenidate against placebo or no treatment, most studies have been conducted over periods of months, in general 3 months or less, with a mean duration of 67 days according to a recent Cochrane review *(34)*. However, there have been some studies suggesting benefits of treatment over longer periods of 12- and 14-month periods *(35, 36)*. Furthermore, more recently there is evidence from a 7-week withdrawal discontinuation study supporting the continued efficacy of methylphenidate after at least 2 years of treatment *(37)*. All these studies will be discussed in detail in Section 8.1 Long-term efficacy.

As is true for all psychotropics, treatment duration cannot be based solely on the evidence from RCTs, as most RCTs last for periods that are much shorter than therapeutic need. It is thus also important to consider 'real world' observational data. A recent study compiled pharmacoepidemiologic surveys of methylphenidate adherence considering population-based databases from Australia, Denmark, Hong Kong, Iceland, the Netherlands, Norway, Sweden, the UK, and the USA *(38)*. It indicated that individuals took methylphenidate for between (median [interquartile range, IQR]) 142 days [42, 473] in the USA (shortest duration) and 426 days [181, 1,037] in Norway and 432 days [130, 1,081] in the UK (longest durations). Over the 5-year follow-up, only 24% (95% confidence interval [CI] 18% to 30%) of children (4-11 years) and 9% (95% CI 6% to 12%) of adolescents (12-17 years) had remained consistently on treatment, with no periods of discontinuation. When accounting for re-initiation, the percentage of children and adolescents covered by treatment raised to 50-60% and 30-40%, respectively. This finding indicates that many individuals re-initiated methylphenidate during the 5-year period, presumably due to recurrent symptoms. Such findings emphasize the need for regular (e.g., at least annual) reassessment of the need for methylphenidate, in line with current best practice, reflected in international and national guidelines, such as the mhGAP guidelines and NICE.

7.3 Requirements to ensure appropriate use of the medicine

To ensure appropriate use of the medicine, ***all*** the following requirements should be met:

7.3.1 Patient eligibility criteria

Patients must be at least 6 years old and younger than 18 years old.

7.3.2 Diagnostic requirements

Patients must have a diagnosis of ADHD according to criteria outlined in ICD-11 or the DSM-5.

As discussed above, the diagnosis of ADHD should be made by a licensed professional with training and expertise in diagnosing ADHD. During the assessment, attention should be paid to psychosocial factors to ensure that symptoms do not merely reflect responses to situational factors that can be rectified. Similarly, a psychosocial perspective can help with the assessment of the degree of impairment across contexts (such as at home, at school, and with peers) that is due to ADHD symptoms specifically. While not a diagnostic requirement in ICD-11 or DSM-5, the mhGAP guidelines recommend that the practitioner should ensure that the symptoms do not respond to measures such as adapting features in the child's environment,

including learning. There are no other diagnostic tests, such as neuropsychological testing, genetic tests, or neuroimaging. Relatedly, the diagnosis cannot be made through symptom rating scales alone.

If history and/or examination suggest risk for cardiovascular disorder (for example, a family history of sudden death or ventricular arrhythmia, high blood pressure), further cardiac evaluation (e.g., electrocardiogram and consultation with cardiology specialist) is needed prior to starting methylphenidate.

7.3.3 Treatment administration requirements and setting

Preparations of methylphenidate are discussed earlier. The medication can be taken at home in the child or adolescent's usual setting. Special restrictions on the prescription of the medication arising from the possible nonmedical use and diversion of methylphenidate are considered in Section 8.5.

7.3.4 Required skill levels of healthcare providers and their availability.

As stated above, patients must be evaluated and diagnosed by, or in consultation with, a specialist -- that is, a professional with training and expertise in the evaluation and treatment of children and adolescents with psychiatric disorders.

The formal training will vary by nation, but mental health care specialists trained in diagnosis and pharmacological treatment of childhood ADHD may include child and adolescent psychiatrists, general psychiatrists, pediatricians, primary care physicians, and in some nations, nurses with specialized training and clinical psychologists.

The requirement for diagnosis and management either by or under supervision by specialists reflects the need to ensure that behavioral symptoms are not better explained by other conditions, do not merely reflect transient responses to temporary situational factors, and cause enough impairment across contexts to warrant medical intervention.

In considering the feasibility of such specialist provision or supervision, we note data from the WHO Mental Health Atlas 2020. It reports that the median number of mental health workers for children and adolescents per 100,000 population ranged between 0.2 workers and 1 worker in all WHO regions apart from the Region of the Americas (8.6 mental health workers per 100,000 population) and the European Region (12.5 mental health workers per 100,000 population). There was also disparity by income group, with 0.01 workers per 100,000 population in low-income countries compared to nearly 20 workers per 100,000 population in high-income countries. Of these workers, psychiatrists were a minority across all settings. Thus, it is important that a broader range of specialists (such as pediatricians, general psychiatrists, primary care physicians, and allied professions) continue to build capacity in the assessment and management of psychiatric disorders, including ADHD, in children and adolescents.

Partly reflecting moves to integrate child and adolescent psychiatric care within primary care settings (in line with Alma-Ata Declaration in 1978 and the Astana Declaration in 2018), there is an increasing capacity for providing pharmacological treatment in primary care settings, when such treatment is indicated. As an example, the proportion of specialists providing training and supervision to primary health care colleagues was high and increasing (81% of countries reporting such supervisory activity in 2020), and the number of primary care centers that offered pharmacological treatment increased (with 39% of countries attaining the target level of 75% of primary care centers offering pharmacological options). Members of the panel preparing this

application confirm that initiatives are underway to upskill relevant practitioners to expand the pool of professionals who are skilled in prescribing and monitoring methylphenidate.
As part of ongoing efforts to scale up child and adolescent mental health provision, the WHO mhGAP guidelines were revised in 2023, and it emphasizes supervision and training by specialists of those in primary care settings to allow a scaling up of the management of childhood mental health conditions. Accordingly, as discussed later, the mhGAP guidelines reinforced the importance to consider the health system's capacity to enforce and implement protocols for ADHD diagnosis, to prescribe and initiate methylphenidate by or in close consultation with a specialist, and to ensure careful clinical monitoring for side-effects, clinical response, adherence, treatment acceptability, and dose adjustment.

SECTION 8: REVIEW OF EVIDENCE FOR BENEFITS AND HARMS.

In this section, we provided a summary of the best available evidence to support the efficacy, effectiveness, and safety of methylphenidate for ADHD in children and adolescents aged 6 to 17 years. Following the instructions for applicants preparing a submission for the 2025 meeting of the WHO Expert Committee, our summary emphasizes control conditions such as no treatment or placebo because there are no medicines specifically included on the WHO Model List of Essential Medicines for the treatment of ADHD in this population group. For completeness, we also summarize findings from head-to-head trials and/or network meta-analysis covering other pharmacological interventions (that are not available in the model list) and/or non-pharmacological interventions.

We prioritized evidence stemming from systematic reviews and meta-analyses. Where not available, we discuss evidence originating from single RCTs and non-randomized and/or observational studies. We highlight studies that were published in 2022 or after, given the evidence summarized in the previous applications in 2019 and 2021.

We also respond to the comments made from expert reviews of the previous application (https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/23rd-expert-committee/a21-methylphenidate) and associated commentary *(39-46)* on the benefits and risks of methylphenidate, specifically regarding:

- the evidence for the efficacy, effectiveness, and safety of long-term (i.e., duration longer than 6 months, and ideally over 12 months) treatment with methylphenidate for children and adolescents with ADHD.
- general concerns about the quality of evidence, particularly those that have been raised by the previous Cochrane reviews, including its recent update in 2023 *(34, 47)*.

For the identification of relevant references based on RCTs and/or meta-analyses of their data, the search terms outlined in **Box 1** were adopted in PubMed, yielding 1,683 records on August 31, 2024. Records had a preliminary screening, and those judged to be relevant were considered for inclusion. For observational studies, we identified records through manual searches in PubMed and Google scholar. In total 46 references - all cited below - are considered as part of the presentation of efficacy, efectiveness, and safety of methylphenidate for children and adolescents with ADHD.

Box 1. Search terms used to identify evidence of benefits and harms in PubMed
(Attention Deficit Disorder with Hyperactivity[mesh:noexp] OR "attention deficit hyperactivity disorder"[tiab] OR "attention deficit disorder"[tiab] OR ADHD[tiab] OR ADD[tiab] OR "hyperkinetic disorder"[tiab] OR HKD[tiab]) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans[mh])) AND (Methylphenidate[mesh:noexp] OR Dexmethylphenidate[mesh:noexp] OR Dexmethylphenidate[tiab] OR Methylphenidate[tiab])

8.1. Long-term efficacy and effectiveness

8.1.1 Randomized controlled trials with treatment duration longer than 6 months

Our literature review identified only two RCTs with a methylphenidate treatment duration of 6 months or longer *(35, 36)*. Both studies were published before the previous application was made

but are discussed in detail in this application in response to concerns over evidence pertaining to longer term benefits and risks of methylphenidate treatment. Details of the studies are given in Table 1.

The Multimodal Treatment of ADHD (MTA) study enrolled 579 children (7 to 9.9 years old) into a RCT for 14 months that contrasted intensive medication management (mostly methylphenidate) with or without intensive behavioral treatment against intensive behavioral treatment only and treatment as usual (referred to the community for treatment, two-thirds of whom received stimulant prescriptions). Of the 289 participants randomized to medication management (in combination with behavioral therapy or alone), 212 (73.4%) remained on methylphenidate for 14 months, with an additional 37 (13.1%) switching per protocol to another medication (mostly dextroamphetamine). Considering the question of whether closely managed medication improved upon the effects of behavioral treatment (combined treatment compared to behavioral treatment), intention-to-treat analyses found that at 14 months those on combined treatment experienced a greater decrease in teacher-ratings of inattention (standardized mean difference [SMD] -0.45; 95% CI -0.7 to -0.2), as well as parent-ratings of inattention (SMD -0.57; 95% CI -0.81 to -0.32), hyperactivity-impulsivity (SMD -0.58; 95% CI -0.82 to -0.33), and aggression (SMD -0.42; 95% CI -0.66 to -0.17) compared to those in behavioral treatment. Combined treatment did not outperform behavioral treatment on teacher ratings of hyperactivity-impulsivity and aggression; classroom observer ratings of hyperactivity-impulsivity and aggression. Methylphenidate was administered at a mean dose of 31.2 mg/d in the combined treatment arm. The largest treatment effects emerged during the first 50-100 days and were maintained until endpoint at 14 months.

This study provides evidence of symptom reduction over 14 months, with some caveats. First, only around 73% of participants randomized to methylphenidate were maintained on this medication at the RCT endpoint, when recommendations for post-study care were made, with the remaining participants being switched to other pharmacological or non-pharmacological intervention. While most of those switches were within the protocol (which was broadly construed as optimal medication management), it nonetheless has an impact on the conclusions pertaining to methylphenidate specifically. Second, the RCT medication management arm was intensive due to monthly 30-minute clinic visits and collection of parent and teacher ratings with dose adjustments as needed; therefore, some effects of the MTA medication treatment arm may be due to non-specific effects of frequent doctor visits. Third, knowledge of intervention could have influenced outcome assessment. However, there are no strong reasons to assume that it did, as empirical data from meta-epidemiological and meta-analytical studies are at odds regarding the extent to which lack of blinding contributes to exaggerated comparative treatment effects, including for subjective outcomes *(48-52)*.

A second RCT conducted in Mexico investigated the effects of methylphenidate for a treatment duration of 12 months. Ninety children aged 6 to 12 years of age with a diagnosis of ADHD were randomized to omega-3/6 fatty acid supplementation, methylphenidate, or their combination. Methylphenidate was administered in a flexible-dose design with mean dose 0.8 mg/kg/day. In intention-to-treat analyses, those taking methylphenidate alongside omega-3/6 showed more improvement compared to those only taking omega-3/6 in ADHD symptoms reported by the parents (SMD -0.51; 95% CI -1.03, 0). Treatment effects of methylphenidate were seen initially in the first 3 months and then maintained throughout the follow-up until the endpoint at 12 months.

This study also had certain limitations. For instance, there were differential rates of discontinuation across arms due to the health status of participants, which may contribute to bias. Specifically, 7% of those taking methylphenidate alongside omega-3/6 and 20% of those only taking omega-3/6 discontinued the study due to adverse events or no efficacy. The absence of blinding in this study may also be a potential limitation *(34)*.

8.1.2 Other relevant randomized controlled trials

Also of relevance to long-term efficacy are RCTs that randomize participants stabilized on methylphenidate to either discontinuation or continuation of medication *(37)*. One such study enrolled 104 youth (ages between 8 and 17 years old) who were taking methylphenidate for a mean of 4.5 years (SD 1.5). These children were then randomized to either continued active medication for 7 weeks or to gradually discontinue to placebo over a 3-week period, which was then followed by 4 weeks of complete placebo. The study found superior outcomes in those who remained on methylphenidate. Specifically, those who stopped methylphenidate showed greater ADHD symptoms severity at endpoint, as rated by teachers (mean difference [MD] -6.6; 95% CI -9.5 to -3.7; SMD -0.52) and investigators (MD -4.6; 95% CI -8.7 to -0.6; SMD -0.23). Relatedly, 40.4% of those randomized into stopping medication had investigator-rated worsening in overall functioning. Three other studies incorporated the randomized discontinuation of methylphenidate and overall found a worsening of symptoms following cessation, providing broad support for the efficacy of stimulants to treat ADHD *(53)*. The length of time that these children had been on methylphenidate varied considerably between study (from one year to a week) and in most studies there was a minority of children and adolescents with ADHD who did not relapse or deteriorate when taken off medications for ADHD. The findings of these randomized discontinuation studies are also limited by features such as participants perhaps being functionally unblinded due to subject-perceived effects of stopping the medicine. Nonetheless, they provide some indirect evidence that methylphenidate may continue to be effective in reducing symptoms in the longer term insofar as symptoms worsen in those randomized to discontinuation (placebo).

8.1.3 Observational studies

Since the last application, two pharmacoepidemiologic studies demonstrated reduced mortality, in particular due to reduced non-accidental injuries, amongst those receiving medicines for ADHD (including methylphenidate) in Sweden and Canada *(54, 55)*.

The first study, conducted in Sweden, adopted a target emulation trial design considering a nationwide cohort of individuals aged 6 through 64 years with an incident diagnosis of ADHD between 2007 and 2018, who were medication naive prior to their diagnosis. Individuals were followed up for 2 years after the ADHD diagnosis, unless they died or emigrated, or until the end date of the study (December 31, 2020). The outcomes were all-cause mortality, as well as natural-cause and unnatural-cause mortality. The crude 2-year all-cause mortality rate was lower among those who initiated ADHD medications within 3 months of the ADHD diagnosis (n = 84,204 individuals) versus those who did not (n = 64,296) (17.3 versus 31.8 per 10,000 individuals). There was only evidence for a reduction in unnatural-cause mortality (-7.4 per 10,000; hazard ratio [HR] 0.75, 95% CI 0.66, 0.86) and no evidence for a reduction in natural-cause mortality (-1.6 per 10,000; HR 0.86, 95% CI 0.71, 1.05). In subgroup analyses, this significant association with lower rates of all-cause and unnatural cause mortality held in children and youth (6-24 years old).

The second study, in Canada, followed a cohort of 217,192 individuals aged ≤ 24 years with a diagnosis of ADHD or who had filled a prescription for an ADHD medication, including methylphenidate, between April 1, 2000 and March 31, 2021. The outcomes were mortality from all causes, unintentional injuries leading to hospitalizations, and unintentional injuries leading to emergency department admissions. The findings indicated that ADHD medication use was associated with reduced risk of all-cause mortality (HR 0.61; 95% CI 0.48, 0.76), unintentional injuries leading to hospitalization (HR 0.71; 95% CI 0.68, 0.75), and unintentional injuries leading to emergency department visits (HR 0.75; 95% CI 0.74, 0.77).

Additionally, a systematic review that was published in 2020 – but was not discussed in previous applications – evaluated the associations between ADHD medications and functional outcomes *(56)*. The review identified 40 studies, mostly register-based case-cohorts. Their findings indicated that methylphenidate was associated with decreased odds of worse academic outcomes (odds ratio [OR] 0.8; 95% CI 0.76, 0.84) and accidental injuries (OR 0.72; 95% CI 0.59, 0.87). There was also some evidence of reduced risk of criminality, although the resulting effect was not statistically significant (hazard ratio 0.87; 95% CI 0.74, 1.02).

8.1.4 Conclusions about evidence for long-term efficacy and effectiveness

There are few RCTs examining long-term treatment (duration > 6 months) of methylphenidate for ADHD in children and adolescents aged 6 to 17 years old, and all had some methodologic limitations. Nevertheless, all available studies point toward reduced severity of ADHD symptoms over long periods of time as rated by parents, teachers, and/or independent investigators.

Causal inferences about methylphenidate cannot be reliably made from observational studies. Nonetheless, available pharmacoepidemiologic data provide important (and perhaps the only possible) evidence of the likelihood of beneficial 'real-world' functional outcomes associated with long-term use of methylphenidate. Such data bolster evidence from RCTs examining long-term effects.

8.2 Short-term efficacy

8.2.1 Core ADHD symptoms

Evidence from RCTs comparing methylphenidate against placebo, mostly of 3 months duration or less, have been extensively reviewed in the prior applications.

However, here we consider a 2023 update of the Cochrane systematic review and pairwise meta-analysis evaluating methylphenidate for ADHD against placebo/no treatment for children and adolescents (aged 18 years and younger) *(34)*.

The updated review included data from 28 additional RCTs compared to the 2015 version of the review. The authors evaluated efficacy considering teacher, independent assessor (mostly clinicians), and parent reports of ADHD symptoms. Most RCTs were conducted in the short-term (mean duration 67 days). This meta-analysis found large treatment effects for methylphenidate over placebo/no treatment for teacher-, independent assessor-, and parent-rated ADHD symptoms. However, the Cochrane review authors rated the overall quality of the evidence for methylphenidate considering teacher-rated symptoms as of 'very low' certainty using the GRADE approach, a concern that has been echoed in the commentary from the Expert Panel in the previous application.

We will first present the key findings and then discuss the quality of evidence and arguments in favor of a higher rating of moderate certainty versus the one of very low certainty that was given by the Cochrane review authors. We will base our rationale on the same data that were presented in the Cochrane review *(34)*.

Teacher-rated ADHD symptoms
The meta-analysis included data from 21 parallel RCTs (including pre-crossover arms), all published prior to 2020, and 1,728 participants. It indicated a moderate-to-large treatment effect in favor of methylphenidate (standardized mean difference [SMD] -0.74; 95% confidence interval [CI] -0.88 to -0.61). There was only low-to-moderate heterogeneity (tau^2 0.03; I^2 38%). There was slight asymmetry at visual inspection of funnel plots, and the Egger regression test was not significant (t -0.23; p 0.81). The quality of evidence was rated in the Cochrane review as "very low", downgraded two levels due to high risk of bias and one level due to moderate statistical heterogeneity.

Independent assessor-rated ADHD symptoms
The meta-analysis included data from 22 parallel RCTs (including pre-crossover arms), including three RCTs published in 2020, and 3,724 participants. It indicated a large treatment effect in favor of methylphenidate (SMD -1.1; 95% CI -1.44 to -0.7). There was high heterogeneity (tau^2 0.58; I^2 95%). There was no assessment of publication bias. The outcome was not graded in terms of quality of evidence.

Parent-rated ADHD symptoms
The meta-analysis included data from 27 parallel RCTs (including pre-crossover arms), all published prior to 2020 and two unpublished studies, and 2,927 participants indicated a moderate treatment effect in favor of methylphenidate (SMD -0.63; 95% CI -0.76 to -0.5). There was moderate-to-high heterogeneity (tau^2 0.06; I^2 58%). There was no assessment of publication bias. The outcome was not graded in terms of quality of evidence.

Ratings of certainty of evidence
As noted above, the evidence for teacher-reported ADHD symptoms was rated as being of 'very low' quality in the Cochrane review. This rating has stimulated discussion, and we summarize below considerations, raised by other researchers, that the evidence should be graded as being of moderate quality *(57, 58)*, particularly in view of recent revisions of the Cochrane risk of basis tools (Risk of Bias 2 tool).

In the Cochrane review, the evidence was downgraded by two levels due to *risk of bias*, specifically a lack of sufficient blinding and selective outcome reporting. Considerations about the impact of blinding were made above when discussing the long-term efficacy in *Section 8.1*. In brief, while we agree that knowledge of intervention *could have* influenced outcome assessment, meta-epidemiologic studies are at odds regarding the extent to which lack of blinding contributes to exaggerated comparative treatment effects, including for subjective outcomes *(48-52)*. The rating of 'high' risk of bias assumes that knowledge of intervention *likely* biased findings and this is not a settled point.

Additionally, it is noteworthy that methylphenidate was efficacious with no significant differences between studies judged to be at low versus high risk of bias (Chi^2 0.13; p 0.71). It has been *(46)* argued that this lack of difference between RCTs at different risk of bias could be

indicative of functional unblinding due to adverse events. In other words, studies that were judged at low risk of bias in the Cochrane risk of bias would actually be of high risk of bias because of 'deblinding'. However, the hypothesis of deblinding is untestable based on the current data and may thus not be suitable grounds for declaring presence of high risk of bias and downgrading of evidence quality.

The Cochrane review also showed that most domain-level ratings across the studies included in the meta-analyses were rated at 'low' or 'unclear' risk of bias (**Figure 1** below is reproduced from the Cochrane review and shows domain-level ratings). The GRADE approach outlined in its handbook recommends that, in this setting, the quality of evidence should either not be downgraded or downgraded by one level.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

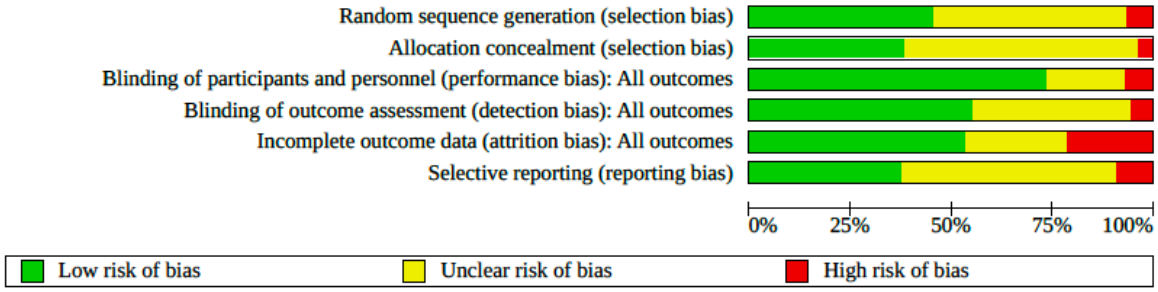

Figure 1. Risk of bias ratings in the Cochrane review *(34)*.

In short, the downgrading of evidence by two levels due to risk of bias alone, could be viewed as overly stringent, subjecting RCTs to a level of scrutiny that is not generally applied across other medications and interventions. Downgrading the quality of evidence by one level due to risk of bias may be more appropriate.

With regards to *heterogeneity*, the decision to downgrade quality of evidence is also arguable as evidence from tau^2 only indicates low-to-moderate heterogeneity considering the empirical distribution of tau^2 instead of solely relying on I^2 *(59, 60)*. The GRADE approach only recommends downgrading the quality of evidence in the presence of large heterogeneity. Therefore, not downgrading quality of evidence may be considered appropriate.

Hence, when considering all of these points together, it could be argued that evidence should be downgraded by one level only due to some concerns about study limitations (risk of bias), and the resulting evidence for the short-term efficacy of methylphenidate against placebo/no treatment measured by teacher-reported ADHD symptoms could be declared to be of "moderate' certainty (see below GRADE table outlining each decision).

Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Relative effect	Certainty
21	Randomised trials	Serious[1]	Not serious[2]	Not serious	Not serious[3]	Not suspected[4]	-0.74 (-0.88, -0.61)	Moderate

1 most information is from studies at low or unclear risk of bias, and potential limitations are likely to lower confidence in the estimates of effect
2 low-to-moderate heterogeneity (tau2 0.03; I2 38%)
3 OIS 580 for Cohen's d 0.3 with alpha 0.05 and beta 0.05 (95% power)
4 No asymmetry in funnel plot; Egger regression test not significant

8.2.3 Other short-term efficacy outcomes.

Since the last application, other systematic reviews and meta-analyses have also considered associations between methylphenidate treatment and both neurocognitive function and academic achievement.

For *neurocognitive functions*, a systematic review and meta-analysis published in 2022 included placebo-controlled trials that investigated methylphenidate in children and adolescents (aged 5-18 years) with ADHD. The study found 31 RCTs comprising 804 people with ADHD and reported that methylphenidate had beneficial effects on all neurocognitive functions (SMD range 0.2 to 0.73). Most studies included those who were prescribed methylphenidate for short periods of time. There was no evidence of heterogeneity (I^2 0%) for all but one cognitive domain. There was no evidence of publication bias considering inspection of funnel plots or the Egger regression test. All studies were rated as having low risk of bias *(61)*.

For *academic achievement*, a systematic review published in 2019 included data from 34 RCTs and 1,777 children (at least 80% of the samples primary school children) with ADHD to assess the comparative effects of methylphenidate against placebo on different academic performance outcomes. For math accuracy, a small effect was found (29 studies; 1528 participants; risk difference [RD] 3%; 95% CI 1.2%, 4.8%); the effect for math productivity was larger, as expected (17 studies; 912 participants; RD 7.8%; 95% CI 4.3%, 11.2%). The effect for number of reading items attempted (five studies; 100 participants; SMD 0.47; 95% CI 0.30, 0.64) was a moderate-sized significant effect in favor of methylphenidate. For reading accuracy, the meta-analysis indicated a small treatment effect that was nonetheless non-statistically significant (nine studies; 207 participants; RD 6.2%; 95% CI -0.9%, 13.4%). For all outcomes, there was no evidence of heterogeneity (I^2 0%) nor publication bias *(62)*. Thus, effects of methylphenidate on academic performance are stronger for productivity than accuracy, but these results were limited to short-term trials between 1 and 7 days and do not test cumulative impact of productivity on longer term achievement. Additionally, academic testing, by its nature, includes high levels of attention and reinforcement in-the-moment and reduces the opportunity to observe effects of medication. As stated earlier, the impracticalities of assigning children to a placebo condition for multiple months creates an ethical barrier to further testing of this question.

For *aggressive behavior* and *emotional dysregulation/irritability*, we did not identify recent systematic reviews or meta-analyses. Intent-to-treat analyses from the Multimodal Treatment Study of ADHD (MTA) indicated that medication management did not differ from community care with regard to irritability across the 14-month RCT *(63)*. There is evidence from uncontrolled trials that aggressive behavior may substantially diminish with methylphenidate treatment *(64, 65)*, but the evidence is very weak in the absence of a randomized control group.

Comparison with other medications licensed for ADHD but not available on the EML or EMLc

A systematic review and network meta-analysis reported on the comparative effects of pharmacological interventions for children and adolescents (ages 5-17 years) with ADHD *(66)*. In terms of head-to-head comparisons, for ADHD core symptoms rated by clinicians closest to 12 weeks, methylphenidate was superior to atomoxetine (-0.22; -0.39 to -0.05, low), but inferior to amphetamines (0.24; 0.05, 0.44, low), and not different from bupropion (-0.18, -0.9 to 0.54, very low), clonidine (0.07, -0.42 to 0.56, very low), and guanfacine (0.11, -0.13 to 0.34, low). For ADHD core symptoms rated by teachers, there were no differences between methylphenidate and bupropion (0.5, -0.17 to 1.17, low) or guanfacine (0.18, -0.86 to 1.22, very low).

In terms of discontinuations due to adverse events, amphetamines (odds ratio [OR] 2.30, 95% CI 1.36–3.89) and guanfacine (2.64, 1.20–5.81) were inferior to placebo in children and adolescents. With respect to tolerability, in children, only amphetamines and guanfacine were less well tolerated than placebo; methylphenidate was not tolerated more poorly than placebo. Therefore, when considering both efficacy and tolerability, the authors of the review concluded that methylphenidate in children and adolescents should be first-line pharmacological interventions for ADHD *(6)*.

8.2.4 Overall conclusions about evidence for short-term efficacy
RCTs indicate that methylphenidate is associated with moderate-to-large (SMD -0.7) reductions of symptoms as rated by teachers, parents and clinicians, and in domains such as academic and neurocognitive functioning.

8.3. Long-term safety

In response to the concerns raised by the previous expert panel, we focus on adverse events that occur in the longer-term on methylphenidate.

8.3.1 Serious adverse events
Both the RCTs of long-term treatment (discussed above) and an observational study of long-term methylphenidate treatment (ADDUCE, discussed below) *(67)* found no association between methylphenidate treatment and serious AEs.

8.3.2 Cumulative exposure concerns
There have been concerns around possible effects on growth and cardiovascular health arising with long-term methylphenidate treatment.

Growth.
It has been hypothesized that methylphenidate might suppress growth, through mechanisms such as the suppression of appetite and hence decreased caloric intake, or endocrine effects *(68)*.

A systematic review and meta-analysis published in 2021 of eighteen observational studies (4,868 participants) evaluated the associations between somatic growth and long-term methylphenidate treatment *(69)*. Average daily dosage of methylphenidate across studies was 29.93 (SD 12.14) and all associations were considered long-term (> 6 months) exposure to the medicine. The meta-analyses indicated statistically significant associations between methylphenidate and decreased height Z-score (SMD -0.27; 95% CI -0.38 to -0.16) and weight Z-score (SMD -0.33; 95% CI -0.44 to -0.22). These estimates translated to slowing of height gain by approximately 1.39 cm and of weight gain by approximately 1.96 kg for a 10-year-old boy over a 2-year period. The most prominent impacts on weight were seen during the first 12 months and on height within the first 24-30 months. These findings indicated that long-term treatment with methylphenidate might be associated with slight growth deficit, particularly for height.

These findings are in line with those reported for the longitudinal cohort established with participants from the MTA, published in 2019 but not discussed in detail in the previous application *(70)*. Specifically, children who were consistently treated with methylphenidate and other stimulants from ages 7-9.9 years through adolescence were found by mean age 24.7 to be,

on average, 4.06 cm shorter than children who were not treated ('negligible') and 2.74 cm shorter than children who were inconsistently treated across the same period.

However, a naturalistic, longitudinal study published in 2023 reported that methylphenidate treatment was not associated with alterations in somatic growth *(67)*. This trans-European observational cohort (henceforth ADDUCE) of 1,410 youth (6-17 years) with ADHD, of whom 756 were treated with methylphenidate, reported on the safety profile of long-term (2-year) methylphenidate treatment. It found no difference in height velocity at any time point between those taking and not taking methylphenidate. Weight velocity showed an initial slowing at 6 months in the methylphenidate group, but no differences were seen after this point. There were no group differences with respect to body mass index (BMI) at any time point.

Other recent studies also argue for caution in asserting causal effects between methylphenidate and reduced growth. Specifically, a recent register-based quasi-experimental and family-based study from Sweden, published in 2023, indicated that ADHD was associated with shorter height before and after ADHD medications were available in the country *(71)*. Additionally, the association between ADHD and shorter height was also partly explained by prenatal factors, psychiatric comorbidities, low socioeconomic status, and shared familial liability between ADHD and short height.

Taken together across these studies, considering methodological limitations collectively, the data suggest that there is value in monitoring growth in order to be aware of any medication-induced changes in height and weight that should be weighed against treatment benefits.

Cardiovascular safety

Because methylphenidate can increase both heart rate and diastolic blood pressure acutely (as discussed below), there have been concerns that, over the long-term, children and adolescents with ADHD receiving this medicine may be at increased risk of cardiovascular events.

Some of the most pertinent data on long-term treatment, not discussed in detail in the previous application, stems from the MTA study *(72)*, which found that, after the 14-month treatment period, children who received combined treatment had a higher heart rate than those treated with behavioral therapy alone at the study endpoint (mean [standard deviation] 84.6 [12.2] versus 79.1 [12], $p = 0.01$). There were no treatment effects on either systolic or diastolic blood pressure.

Considering observational studies, a systematic review and meta-analysis published in 2022 synthesized evidence on possible associations between methylphenidate (and other ADHD medications) and a broad range of cardiovascular events *(73)*. Nineteen studies and 3,931,532 participants were included across the analyses. Of these, 14 were cohort studies, and the median follow-up time was 1.5 years (range 0.25, 9.5 years). Pooled adjusted relative risk (RR) did not show statistically significant associations between ADHD medication use and any cardiovascular events among children and adolescents (RR 1.18; 95% CI 0.91, 1.53). Unfortunately, tau^2 was not provided, which limits the extent to which inferences on heterogeneity can be made considering the large number of participants included in the analyses *(59)*. There was no evidence of publication bias.

More recently, ADDUCE (described above) *(67)* reported a greater increase in systolic and diastolic blood pressure in the methylphenidate group compared with the no-methylphenidate group at 6, 12, and 24 (but not 18) months from baseline. Pulse rate increased more in the methylphenidate group than in the no-methylphenidate group at 12 and 24 months, but not at 6 or 18 months.

Also more recently, a Swedish register-based investigation evaluated the long-term outcomes of methylphenidate (and other ADHD medications) in a case-control study nested within a cohort of 258,835 individuals with ADHD aged 6 to 64 years living in Sweden (2007-2020) *(74)*. All cases with an incident diagnosis of any cardiovascular disease (including ischemic heart diseases, cerebrovascular diseases, hypertension, heart failure, arrhythmias, thromboembolic disease, arterial disease, and other forms of heart disease) were identified. The analysis retained 10,388 individuals with ADHD who had a cardiovascular event, and those were demographically matched with 51,672 individuals with ADHD and without a cardiovascular event. Both case and control groups had a median follow-up period of 4.1 years (IQR 1.9, 6.8). In line with the findings from the systematic review, there were no differences across groups regarding previous ADHD medication use (83.9% versus 83.5% in cases and controls, respectively). Methylphenidate was the most dispensed medication (76.2% and 76.1% were users amongst cases and controls, respectively). However, when considering cumulative duration of medication use, there was evidence for an increased risk of cardiovascular events with longer cumulative duration of ADHD medication use compared to nonuse (OR [95% CI] 0 to ≤1 year: 0.99 [0.93, 1.06]; 1 to ≤2 years: 1.09 [1.01, 1.18]; 2 to ≤3 years: 1.15 [1.05, 1.25]; 3 to ≤5 years: 1.27 [1.17, 1.39]; >5 years: 1.23 [1.12, 1.36]). This finding was similar when focusing on children, adolescents, and young adults (age < 25 years old) versus older adults (age ≥ 25 years old). When considering specific cardiovascular events, a significant association was found for hypertension and arterial disease, but not arrhythmia, heart failure, ischemic heart disease, thromboembolic disease, or cerebrovascular disease. Additionally, associations were only seen at the higher doses, albeit those analyses were not stratified between children/adolescents and adults.

To address the potential issue of unmeasured confounding in between-person analyses, a follow-up population-based Swedish register study adopted a self-controlled design and compared rates of cardiovascular events (ischemic heart disease, cerebrovascular, thromboembolic, heart failure, arrythmias) 1 year before methylphenidate and after 6 months of methylphenidate treatment *(75)*. In Bayesian analyses, there was evidence of a 10% increased risk of cardiovascular events in individuals receiving methylphenidate compared with matched controls after 6 months of treatment. The probability of finding a methylphenidate related difference in risk decreased when considering risk levels of 20% or larger. The authors of this study interpreted the findings as indicative of a small, not marked, elevation in risk in those taking methylphenidate for 6 months. This study did not consider children (only 12 years and above were included) and lacked data on dosage effects (which emerge as important in other studies of cardiovascular risk).

Taken together across these studies, considering methodological limitations collectively, once again the data suggest that there is value in monitoring cardiovascular parameters (e.g., heart rate, blood pressure) in order to be aware of any medication-induced changes in the cardiovascular system that should be weighed against treatment benefits.

8.3.3 Psychiatric/neurological adverse events

In ADDUCE, <u>*suicidal ideation and behavior*</u> was not associated with methylphenidate (3.17% in the methylphenidate group and 0.77% in the no methylphenidate group at 6 months, a non-significant difference after adjusting for baseline differences across groups) *(67)*. The finding that methylphenidate treatment was not associated with increased suicidal behavior is in line with evidence from register-based studies *(76)*.

Additionally, parent- and child-ratings of ***mood*** improved in those taking methylphenidate compared to the no methylphenidate group after 24 months of treatment in ADDUCE *(67)*.

Lastly, the prevalence of ***psychotic-like symptoms*** decreased for both groups and there were no significant differences between groups in ADDUCE *(67)*. These data align with the evidence from Swedish registry studies that do not support an association between methylphenidate and psychosis when comparing periods on- and off-medicine within an individual *(77)*.

8.4. Short-term safety

8.4.1. Non-serious adverse events

The Cochrane review published in 2023 *(34)* included data from 35 parallel RCTs (including pre-crossover arms) and 5,345 participants. It indicated a 23% higher risk of non-serious adverse events with methylphenidate compared to placebo (relative risk [RR] 1.23; 95% CI 1.11, 1.37). Heterogeneity was judged substantial (tau^2 0.05, I^2 72%). The quality of evidence was classified as "very low", downgraded two levels due to high risk of bias and one level due to moderate statistical heterogeneity.

With regard to specific groupings of non-serious adverse events, there was increased risk for the following non-serious adverse events:

- Nervous system
  - Headache (32 trials; 5,041 participants; RR 1.33; 95% CI 1.04, 1.70)
  - Tension (1 trial; 60 participants; RR 23; 95% CI 1.42, 373.44)
- Digestive system
  - Decreased appetite (30 trials; 5,127 participants; RR 3.35; 95% CI 2.49, 4.50)
  - Decreased weight (dichotomous) (11 trials; 2,001 participants; RR 5.44; 95% CI 2.47, 11.98)
  - Decrease in weight (continuous) (7 trials; 1,400 participants; SMD -1.13; 95% CI -1.4 to -0.85)
  - Decrease in body mass index (BMI) (3 trials; 810 participants; SMD −1.00; 95% CI −1.26 to −0.73)
  - Dry mouth (4 trials; 1057 participants; RR 3.79; 95% CI 1.26, 11.39)
- Cardiovascular system
  - Pallor (1 trial; 60 participants; RR 23; 95% CI 1.42, 373.44)
  - Increase in pulse (13 trials; 2,205 participants; MD 3.86; 95% CI 2.09, 5.63)
  - Increase in diastolic blood pressure (13 trials; 2,032 participants; MD 1.90; 95% CI 0.68, 3.11)
- Sleep
  - Trouble sleeping or sleep problems (15 trials; 2,620 participants; RR 1.62; 95% CI 1.18, 2.21)
  - Insomnia (15 trials; 2,315 participants; RR 1.90; 95% CI 1.12, 3.22)
  - Lower sleep efficiency percentage (time spent asleep while in bed) after treatment discontinuation (1 trial; 48 participants; MD 5.42; 95% CI 0.21, 10.63)
- Other
  - Excoriation (chronic skin-picking) (2 trials; 389 participants; RR 3.22; 95% CI 1.20, 8.64)

Importantly, *there was also no evidence of an association between several other non-serious adverse events and methylphenidate*. A comprehensive list of those is reported in "Analyses 7" of the Cochrane review (see pages 733 to 774 of the PDF document of the full review).

Certainty of evidence

As outlined below, we believe that "moderate" would be more appropriate classifications for the quality of evidence that was presented (see below GRADE table outlining each decision).

- With regard to the *risk of bias*, the ratings were not calculated specifically for the non-serious adverse events, and the extent to which it is sensible to extrapolate those from the efficacy outcomes is unclear. Additional considerations regarding risk of bias were also made above and are generally appropriate for this section as well. Taken together, it could be proposed as more appropriate that quality of evidence should not be downgraded, or at most it should be downgraded one level.
- With regard to *heterogeneity*, a subgroup analysis indicated that stratified analyses by doses only found significant increased risk of non-serious adverse events in studies using high doses compared to low doses (RR [95% CI] 1.23 [1.14, 1.32] versus 1.02 [0.97, 1.07]) and there was no residual heterogeneity within each subgroup (tau^2 0, I^2 0). This difference across subgroups was statistically significant (Chi^2 18.52, $p < 0.0001$). The findings from the subgroup analysis are highly convincing considering evidence of dropouts due to side effects (see below). It could be proposed as more appropriate that quality of evidence should not be downgraded and that the estimates of the subgroup analyses should be considered.

Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Relative effect	Certainty
35	Randomised trials	Serious[1]	Not serious[2]	Not serious	Not serious[3]	Not suspected[4]	1.23 (1.11, 1.37)	Moderate

1 most information is from studies at low or unclear risk of bias, and potential limitations are likely to lower confidence in the estimates of effect
2 heterogeneity could be explained by analyses accounting for doses, and the subgroup analyses are of high credibility
3 OIS 1,310 for placebo proportion (437 in 1,000) and methylphenidate proportion (538 in 1,000) with alpha 0.05 and beta 0.05 (95% power)
4 Not formally assessed.

8.4.2. Serious adverse events

The Cochrane review published in 2023 *(34)* included data from 26 RCTs (including pre-crossover arms) and 3,673 participants, mainly of short-term treatment studies. It indicated no association between methylphenidate and serious adverse events (RR 0.8; 95% CI 0.39, 1.67). The lack of association held for all bodily systems (see pages 720 to 723 of the PDF of the 2023 Cochrane review). There was no evidence of heterogeneity (tau^2 0, I^2 0). The quality of evidence was classified as "very low", downgraded two levels due to high risk of bias and two levels due to imprecision of the resulting effect size.

As serious adverse events are rare, evidence from observational studies is considered for a comprehensive assessment of safety. A study population registry study from Hong Kong including 29,604 individuals aged 6-25 years who were prescribed methylphenidate between Jan 1, 2001, and Dec 31, 2017 evaluated the associations between methylphenidate use and *seizures* through a within individual analysis *(78)*. While seizures were a rare event, there was an

increased risk during the first 30 days of methylphenidate treatment compared with that during non-exposed periods, with an incidence rate ratio of 4.01 (95% CI 2.09, 7.68). However, no increase in risk was identified in the longer term- both during the following 31–180 days of treatment (1.13; 0.56, 2.25) or during subsequent treatment (1.38; 0.92, 2.07).

8.4.3 Discontinuations due to adverse events

Some systematic reviews and meta-analyses have also examined discontinuations due to adverse events as a proxy for tolerability *(66)*. To some extent, this outcome may indicate the perceived risk-benefits of treatment in light of adverse events: if adverse events are more important than treatment benefits, participants in RCTs may discontinue the intervention because of adverse events.

A systematic review and meta-analysis published in 2022 was conducted to evaluate the impact of methylphenidate dose and schedule (fixed versus flexible) on treatment outcomes in RCTs *(79)*. A total of 57 placebo-controlled RCTs involving 5,414 children and adolescents aged 5-18 years with ADHD were included. There was evidence for a significant dose-response association between stimulant dose and dropouts due to adverse events in fixed-dose trials, with a log-linear association indicating constant increments, on an exponential scale, in the risk of discontinuing treatment due to an adverse event for every 1 mg increase in dose of methylphenidate. These findings align with the evidence discussed above that the risk of adverse events may be more pronounced at higher doses. Additionally, a previous review found that methylphenidate did not differ significantly from placebo in rates of discontinuation due to adverse event (OR 1.44; 95% CI 0.90, 2.31) *(66)*.

A systematic review and network meta-analysis reported on the comparative effects of pharmacological interventions for children and adolescents (ages 5-17 years) with ADHD also considered some adverse events *(66)* that included all-cause discontinuation rates, discontinuation rates due to adverse events, as well as changes in weight and blood pressure. It concluded that methylphenidate in children and adolescents should be first-line pharmacological interventions for ADHD, as its tolerability profile was more favorable than other medications used for childhood ADHD, particularly amphetamines and guanfacine *(66)*.

8.5 Substance misuse

8.5.1. Nonmedical use and diversion

Nonmedical use of methylphenidate refers to its use for purposes other than those medically intended, and it includes misuse for recreational purposes and/or performance enhancement without a physician prescription. Diversion is defined as the channeling of methylphenidate from legal sources to the illicit marketplace (including sharing, selling, and trading with individuals who plan to use it without a prescription).

A systematic review *(80)* of all literature on the nonmedical use and diversion of prescription stimulants identified 86 studies addressing the epidemiology of nonmedical use of stimulants and/or diversion. Rates of these behaviors varied widely across studies and generally focused on older adolescents and college students, finding prevalence rates of nonmedical use ranging from 2.1% to 58.7% and diversion ranging from 0.7% to 80.0%.

However, it is critical to recognize that nonmedical use, while important to monitor due to the reality of serious adverse events, largely consists of young adults (university-age) who use infrequently and at times of academic stress. For example, in the College Prescription Drug

Study in the US (19,539 participants), most (84%) endorsing any nonmedical use in their lifetimes (15.9%) reported past 12 months use (10%) between 0-9 times *(81)*. While fewer data are available on this topic at younger ages, the Monitoring the Future national survey study in the US has been helpful in this regard *(82)*. From datasets collected across 3,284 US secondary schools between 2005-2020, mean past year nonmedical use of prescription stimulants amongst 231,141 students was 5.7% at the school level and 6.0% at the individual level. Multiple variables were associated with nonmedical use (e.g., other substance use such as marijuana and alcohol, parental college education, greater percentage of student body identifying as White; greater percentage of student body using prescribed stimulant medications). Prevalence of methylphenidate use without a doctor's orders, reported to 2023 from the Monitoring the Future study, has indicated a marked decline from a 2001 (year of first tracking) to 2024, from 2.9% to 0.6% of 8th graders, 4.8% to 0.5% of 10th graders, and from 5.1% to 0.6% of 12th graders (final grade before university) *(83)*.

While most nonmedical use has been associated with no, or minor, medical effects, adverse medical outcomes, including serious adverse events, have occurred in some individuals, particularly when administered by non-oral routes. Making use of data from America's Poison Centers database, National Poison Data System, the US FDA in 2023 reported that the most severe harms from nonmedical use of stimulants were from a non-oral route (injection or nasal/inhalation) *(84)*. Clinical effects of stimulant overdose can include cardiovascular effects ranging from hypertension and agitation to sudden cardiac death. The latest available United States Drug Abuse Warning Network (DAWN) release for 2022 (https://store.samhsa.gov/sites/default/files/pep23-07-03-001.pdf) provides data on drug-related emergency department visits by substance. Weighted estimates that did not make the top six most frequent drug-related causes of ED visits (alcohol, opioid, cannabis, methamphetamine, cocaine, and benzodiazepine) were excluded; stimulants were among these.

Multiple communities and agencies, including regulatory bodies, the medical community, and researchers have taken action to prevent both the nonmedical use and diversion of psychostimulants. While the steps taken vary by nation, methylphenidate is considered a 'controlled' substance in many countries, and its prescribing and dispensation is subject to restrictions that aim to minimize both diversion and nonmedical use. These controls include the following measures on the side of the prescriber:

- Special training and licensure requirements for prescribing methylphenidate;
- Monitoring of prescription rates by regulatory authorities to 'flag' excessively high, unexplained rates of prescriptions;
- The inability to issue 'refill' prescriptions;
- Requirement for regular monitoring and ongoing assessments of the need for the medication;
- The prescription of formulations that may have less nonmedical use potential.

Additionally, multiple recommendations outside of regulatory steps have been offered in clinical and research literature, by agencies such as the U.S. DEA and professional organizations, studies testing reduction of nonmedical use and diversion (e.g., prescribe extended release instead of immediate release formulations) *(80, 85-87)*, and studies testing training programs for physicians designed to aide their prevention or reduction of stimulant diversion and misuse *(88, 89)*. These recommendations center on educating parents and youth of the dangers of both activities as well as attending to prescribing behaviors and patient behaviors that have the potential to elevate risk (e.g., accumulating unused pills, storing medication in visible locations).

In addition, many entities, formed by those living with ADHD, their families and friends, have produced materials to educate parents on how to prevent nonmedical use and diversion. For example (https://www.additudemag.com/adhd-medication-diversion-teens-sharing-stimulants/). The measures suggested center on the need for education by the provider to the parent, and the parent to the child.

Overall, the consensus in the literature has been that the benefits of methylphenidate continue to outweigh the risks when used to treat children and adolescents aged 6-17 with ADHD.

8.5.1 Risk of later substance use after stimulant treatment

With regards to the concern that methylphenidate may be associated with substance use across development, evidence from the MTA and other observational studies indicate that there is no evidence of an association between methylphenidate in childhood and an increased risk for substance use in adolescents and young adults with childhood ADHD *(90-92)*. Large epidemiologic studies have found protective effects for substance use outcomes of medications for ADHD (that included stimulants) in which within-subjects analyses have compared medicated and unmedicated periods, allowing control for confounding by indication *(92)*. For example, in an analysis of commercial healthcare claims in the US between 2004 and 2014 for 2,993,887 adolescent and adult patients with ADHD, male and female patients had 35% and 31%, respectively, lower odds of concurrent referrals to emergency departments for substance-related events. Following up on remaining concerns about confounding variables and other issues (e.g., missing measurement of harmful substance use that fails to present to a hospital), the MTA analyses adjusted for time-varying confounders when studying the association between stimulant treatment through adolescence and later substance use or substance use disorder and found no statistically significant associations that survived correction for experiment-wise error (97). Although none of these studies can claim to have protection of bias by random assignment and blind placebo-controlled conditions for the multiple years between childhood and adulthood when substance use/disorder typically occurs, these studies collectively fail to provide support for increased risk of substance use/disorder for the average childhood patient taking stimulants to treat ADHD. Further data on the progression to misuse amongst youth prescribed stimulants comes from the Monitoring the Future study dataset. In this study, initiation of stimulant treatment for ADHD in childhood was not associated with elevated substance use risk, defined as cocaine, methamphetamine, or prescription stimulant misuse in adolescence *(93)*. However, initiation of stimulant treatment at older ages (greater than or equal to age 10) and for shorter duration was associated concurrently with higher odds of past-year cocaine or prescription stimulant misuse in adolescence than those initiating treatment in childhood. As noted by the authors, causal relations could not be concluded based on the methodology (self-reported survey retrospective data). In addition, inability to account for the wealth of confounders that might drive late-initiating treatment (persistent ADHD symptoms; elevated urgent need for treatment due to heightened impairments including pre-existing substance use) are important to consider.

8.6 Summary

Benefits

Long-term (over periods of 6 months) methylphenidate treatment has moderate effects in reducing core ADHD symptoms, as assessed by parent, teacher, and independent assessors (i.e.,

clinicians). These benefits are smaller than those noted in meta-analyses of shorter-term RCTs (mostly under 3 months). The quality of evidence in favor of long-term effects is also weaker than that in favor of short-term effects.

RCTs conducted in the short-term also note benefits on educational performance and neurocognitive functioning. Additionally, observational studies, including those evaluating long-term methylphenidate treatment, suggest association with reduced mortality and fewer accidental injuries, among other beneficial functional/direct outcomes.

Harms

Neither long-term nor short-term methylphenidate treatment has been associated with serious adverse events in RCTs or observational studies. There is mixed evidence concerning the impact of cumulative, long-term treatment with methylphenidate and alterations in somatic growth, and limited evidence from one study on increased risk for seizures in the first month of treatment. Observational studies on cardiovascular risk are inconclusive, with some finding no increase and others reporting modest increases in risk, particularly in association with higher doses. This evidence should be discussed and weighed against treatment benefits in shared decision-making.

Comparison with other conditions

The magnitude of the treatment effects estimated in meta-analyses of methylphenidate is large, particularly when compared to other pharmacological and non-pharmacological interventions in psychiatry *(94)*.

Additional considerations

We presented data to support a rating of at least moderate certainty of evidence for short-term effects. We acknowledge that there is less evidence of long-term effects, and the certainty of evidence is thus weaker compared to the short-term effects. While more evidence from long-term RCTs is certainly desirable, RCTs involving placebo over periods of one year or longer are logistically challenging and unlikely to attain ethical approval given the current state of evidence in support of methylphenidate, even if imperfect. Additionally, to address some concerns about risk of bias arising from unblinding through adverse events would require the use of a nocebo (that is, an inactive agent with adverse events matching those of methylphenidate), which would again raise further ethical concerns. In this context, evidence from other designs, such as randomized discontinuation trials and observational studies constitute the best available evidence for long-term effects and should be considered.

SECTION 9: SUMMARY OF RECOMMENDATIONS IN CURRENT CLINICAL GUIDELINES.

9.1 Recommendations in existing WHO guidelines

9.1.1 Mental Health Gap Action Program (mhGAP)

The WHO mhGAP guideline published in 2023 updated its previous recommendation regarding the effectiveness and safety of pharmacological interventions for children with a diagnosis of attention-deficit/hyperactivity disorder.

In its latest version, WHO mhGAP recommends that, for children 6 years old or older and adolescents who have ADHD, methylphenidate may be considered provided that:

- A careful assessment of the child/adolescent has been conducted.
- ADHD symptoms are still causing persistent significant impairment in at least one domain of functioning (education, relationships, occupation), after the implementation of environmental modifications in schools, at home, or in other relevant settings/
- The child/adolescent and the caregivers, as appropriate, have been informed about ADHD treatment options and supported in decision-making.
- Methylphenidate prescription is made by, or in consultation with, a specialist.

The mhGAP guideline reinforces that methylphenidate should be offered only in the context of a management plan that addresses psychosocial risks and vulnerabilities and environmental factors that have an impact on symptoms, functioning, well-being, and participation of children and adolescents with ADHD. Additionally, whenever possible methylphenidate treatment should be combined with brief parent behavioral therapies. Children and adolescents receiving methylphenidate should be maintained under close clinical monitoring for improvement in symptoms and prevention of adverse events. A specialist care provider trained on management of ADHD should reassess the child's/adolescent's management plan for ADHD at least once per year.

The treatment plan for children and adolescents with ADHD should also include psychosocial interventions that may attenuate the impairment stemming from symptoms, such as organizational skills training (strongly recommended) and social skills and cognitive training (conditionally recommended).

As for all child mental health care, the child/adolescent and parent/caregivers, as appropriate, should be informed about ADHD treatment options and supported in decision-making regarding both non-pharmacological and pharmacological management.

9.2 Recommendation sin other current clinical guidelines

A comprehensive overview of the guidelines from the US, Europe, and Asia have been previously provided in other studies *(95, 96)*. The guidelines come from distinct cultures with very different healthcare systems, varying rates of diagnostic identification, and differing availability of both pharmacological and non-pharmacological interventions. We highlight below a couple of those that combined rigorous assessments of the evidence (through systematic reviews and critical appraisal of the evidence) and expert opinion.

9.2.1 American Academy of Pediatrics (APA), the US *(97)*

The guidelines are addressed to pediatricians or other primary care clinicians (PCCs) and state that PCCs may benefit from additional consultative support and guidance from child and

adolescent psychiatrists, clinical child psychologists, developmental/ behavioral pediatricians, neurodevelopmental disability physicians, child neurologists, or child- or school-based evaluation teams.

The guidelines provide recommendations on the assessment and diagnosis, psychosocial interventions, medication and monitoring, interventions in educational settings, organization of care, and implementation.

The guidelines were based on an independent systematic review of the evidence, with the search limited to research published before 2016. Critical appraisal of evidence was done considering AAP policies.

For children 6-11 years of age, FDA-approved medications for ADHD should be prescribed along with parent- and/or teacher-administered behavioral therapy (preferably both parent- and teacher-administered interventions).

For adolescents 12-17 years of age, FDA-approved medications for ADHD should be prescribed. Practitioners are *encouraged* to prescribe evidence-based training interventions and/or behavioral interventions (if available). Educational interventions and individualized instructional supports, including school environment, class placement, instructional placement, and behavioral supports, are a necessary part of any treatment plan.

Albeit any FDA-approved medicine for ADHD is recommended, there is recognition that the evidence is particularly stronger for stimulants (including methylphenidate) compared to other non-stimulant medicines.

9.2.2 National Institute for Health and Care Excellence (NICE), United Kingdom *(2)*

The guidelines consider that diagnosis should be made by specialist psychiatrist, pediatrician, or other appropriately qualified healthcare professionals with training and expertise in ADHD diagnosis, working in multi-disciplinary ADHD services. Prescribing can be shared with primary care physicians, and there should be formal shared care arrangements.

The guidelines provide recommendations on the assessment and diagnosis/recognition, information and support, psychosocial interventions, medication and monitoring, interventions in educational settings, dietary interventions, and organization of care.

The guidelines were based on an independent systematic review of the evidence and GRADE was adopted to assess the evidence.

For school aged children (age $\geq$ 5 years) and adolescents, it is recommended that ADHD-focused support (e.g., education and information on the causes and effects of ADHD, advice on parenting strategies, and liaison with school) is recommended at the first moment. If ADHD symptoms and related impairment persist in at least one area of functioning after these environmental modifications, there is recommendation that methylphenidate be started as the first-line treatment. For children, if there is comorbid oppositional defiant disorder or conduct disorder, parent training programs should be added. For adolescents, if symptoms are still impairing after the start of medicine, cognitive-behavioral treatment should be added.

SECTION 10: SUMMARY OF AVAILABLE DATA ON COMPARATIVE COST AND COST-EFFECTIVENESS.

Table 1 provides a summary of the costs (in US dollars, USD) of methylphenidate in different countries. These numbers were extracted from National websites considering those available in the WHO Pharmaceutical Market Information Sources *(98)*.

Table 1. Prices of methylphenidate in different countries across the world.

Country	Medicine and strength	Package	Price (in USD)	Price per unit (USD)
Brazil	Methylphenidate hydrochloride 10 mg	Pack 30 tablets	4.89	0.163 per tablet
Malaysia	Methylphenidate hydrochloride 10 mg	Pack 30 tablets	26.97	0.899 per tablet
Peru	Methylphenidate 10 mg	Package 100 tablets	24.76	0.24 per tablet
Portugal	Methylphenidate 10 mg	Package 30 capsules	8.35	0.28 per capsule
South Africa	Methylphenidate 10 mg	Package 30 tablets	8.68	0.28 per tablet
Spain	Methylphenidate hydrochloride 36 mg	Package 30 capsules	23.84	0.79 per capsule
Sweden	Methylphenidate hydrochloride 10 mg	Package 30 tablets	13.04	0.43 per tablet
UK	Methylphenidate 10 mg	Package 30 tablets	2.95	0.098 per tablet
USA	Methylphenidate hydrochloride 10 mg	Package 100 tablets	14.28	0.14 per tablet
Vietnam	Methylphenidate hydrochloride 10 mg	Box of 3 blisters x 10 tablets	0.85	0.028 per tablet

Because there are no other medicines in the model list that can be adopted for the treatment of ADHD in children and adolescents, we did not provide a comprehensive overview of comparative costs. However, since this is required in the instructions for submissions to the Model List, we added below evidence for comparative costs of different medicines based on the data from the US (**Table 2**). While this is a superficial assessment, it provides good evidence that methylphenidate is cheaper than possible therapeutic alternatives for which the evidence of benefits and harms is not as strong.

Table 2. Price of medicines approved by the FDA for the treatment of ADHD in the US.

Medicine	Medicine and strength	Package	Price (in USD)	Price per unit (USD)
Methylphenidate	Methylphenidate hydrochloride 10 mg	Package 100 tablets	14.28	0.14 per tablet
	Dexmethylphenidate hydrochloride 10 mg	Package 100 tablets	34	0.34 per tablet
Amphetamines	Mixed amphetamine salts 5 mg	Package 100 capsules	89.59	0.9 per capsule
	Lisdexamfetamine 30 mg	Package 90 capsules	464.44	5.16 per capsule
Atomoxetine	Atomoxetine 40 mg	Package 30 capsules	37.04	1.23 per capsule
Guanfacine	Guanfacine hydrochloride 2 mg	Package 100 tablets	29.37	0.28 per tablet

Data from https://www.vendorportal.ecms.va.gov/nac/Pharma/List

There is no robust evidence to indicate that the prevalence of ADHD varies based on geographic region or income level (see above, section "6.2 Epidemiology"). Therefore, the impact of treatment of ADHD with methylphenidate should be comparable across countries (as indicated in Table 1, range between USD 0.1-0.9 per tablet of methylphenidate hydrochloride 10 mg). Costs may vary depending on the formulation, manufacturer, or both.

We could not find additional evidence in terms of the cost-effectiveness of methylphenidate compared to what has been outlined in the previous application. Therefore, the information below is essentially a reproduction from what was already presented in the latest application considering the pieces of information that focused on methylphenidate specifically.

The MTA evaluated the cost-effectiveness of ADHD treatments and reported that medication management was the least expensive treatment (compared to behavioral treatment and combined treatment) and more cost-effective than combination treatment and behavioral treatment alone *(99)*. Specifically, the incremental cost-effectiveness ratio (ICER) for medical management versus community care was $360, indicating that it cost that amount for each of the children brought to normal functioning by treating them through medication management, and they would not have been brought to normal functioning by treating them through usual care in the community.

A Markov model was constructed to compare immediate release methylphenidate versus no treatment from the perspective of the Brazilian Unified Health System as payer, and the time horizon was 6 years *(100)*. Considering the immediate release methylphenidate, monthly cost of Int$38, the ICER of treatment was Int$9,103/QALY for children and I$11,883/QALY for adolescents. In a two-way sensitivity analysis, considering one Gross National Product per capita (I$11,530) as willingness-to-pay, a cost of no-treatment lower than I$45/month would render immediate release methylphenidate a cost-saving strategy.

A systematic review of three studies published in 2005 evaluated the cost-effectiveness of methylphenidate. It indicated that methylphenidate is a cost-effective treatment option *(101)*. In the first study, the costs per each additional quality-adjusted life year (QALY) gained with

methylphenidate versus no treatment ranged from $15,509 to 19,281 considering short- and medium-term benefits of methylphenidate. In the second study, the costs per each additional QALY gained with methylphenidate treatment versus no treatment was $27,766. In the third study, costs per each additional point in the Conners Teacher Rating scale gained with methylphenidate treatment was $93, or $560 for a 6-point gain.

Another systematic literature review published in 2012 evaluated the economics of pharmacotherapies for ADHD. Searches were conducted in MEDLINE, the National Health Services (NHS) Economic Evaluation database, and EMBASE *(102)*. Studies were eligible if they compared two or more ADHD interventions (at least one pharmacotherapy), assessed both costs and outcomes, and were conducted between 1990 and 2011 in North America, Europe, Australia, or New Zealand. Thirteen papers were included and pharmacotherapies, including methylphenidate, were found to be cost-effective compared with no treatment, placebo, behavioral therapy, or community care among children and adolescents with ADHD.

Lastly, a systematic review of the literature published in 2013 described the cost-effectiveness analyses of medications launched in Spain for the treatment of ADHD *(103)*. A search was conducted in PubMed/MEDLINE, SCOPUS, databases of the Centre for Reviews and Dissemination, and the websites of technology assessment agencies from Canada, the United Kingdom, and Spain. Eleven studies that considered at least methylphenidate or atomoxetine in children/adolescents with ADHD were examined. Methylphenidate was presented as cost-effective over placebo or no treatment in all studies.

SECTION 11: REGULATORY STATUS, MARKET AVAILABILITY AND PHARMACOPOEIAL STANDARDS.

At least 53 countries (including LMICs such as Botswana, Colombia, Ghana, Honduras, Indonesia, Mexico, Peru, Tonga, Tunisia, Uganda, Uruguay, among others) currently include methylphenidate in their national essential model lists (available from https://global.essentialmeds.org/dashboard/medicines/1196). It is possible that the number of countries is higher as several have recently updated their national essential model lists.

Methylphenidate is approved for use in various jurisdictions as follows:

- Australia
- Argentina
- Bangladesh
- Belgium
- Brazil
- Canada
- Chile
- Colombia
- Costa Rica
- Cote D'Ivore
- Cyprus
- Czech Republic
- Denmark
- Dominican Republic
- El Salvador
- Estonia
- Ethiopia
- France
- Gambia
- Germany
- Ghana
- Great Britain
- Greece
- Guatemala
- Guinea
- Honduras
- Iceland
- India
- Indonesia
- Iran
- Iraq
- Ireland
- Israel
- Japan

- Jordan
- Kenya
- Kuwait
- Lebanon
- Liberia
- Libya
- Mali
- Mexico
- Malaysia
- Morocco
- New Zealand
- Nicaragua
- Niger
- Nigeria
- Norway
- Oman
- Pakistan
- Panama
- Paraguay
- Peru
- Poland
- Portugal
- Republic of Korea
- Senegal
- Sierra Leone
- Slovenia
- Spain
- South Africa
- Sri Lanka
- Sudan
- Sweden
- Switzerland
- Syria
- Tanzania
- Tunisia
- Uganda
- Uruguay
- USA
- Venezuela
- Yemen
- Zambia
- Zimbabwe

Availability of Pharmacopeial Standards for Methylphenidate

- British Pharmacopoeia: Yes (https://www.pharmacopoeia.com)
- European Pharmacopoeia: Yes (https://www.edqm.eu/en/european-pharmacopoeia)
- Indian Pharmacopoeia: Yes (https://www.indianpharmacopoeia.in)
- United States Pharmacopoeia: Yes (http://www.usp.org)
- Japanese Pharmacopoeia: Yes (https://www.pmda.go.jp/english/index.html)

Section 12: Reference list.

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