Methylphenidate

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 24. Medicines for mental and behavioural disorders

EMLc | ATC codes: N06BA04

Indication	Attention deficit hyperactivity disorder ICD11 code: 6A05
INN	Methylphenidate
Medicine type	Chemical agent
List type	Complementary (EML) (EMLc)
Formulations	Oral > Solid > tablet: 5 mg (hydrochloride) ; 10 mg (hydrochloride) ; 20 mg (hydrochloride) ; 18 mg extended-release (hydrochloride) ; 27 mg extended-release (hydrochloride) ; 36 mg extended-release (hydrochloride) ; 54 mg extended-release (hydrochloride) ; 72 mg extended-release (hydrochloride) Oral > Solid > capsule: 10 to 60 mg extended-release (hydrochloride)
EML status history	Application rejected in 2019 (TRS 1021) Application rejected in 2021 (TRS 1035) Application rejected in 2025 (TRS 1064)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Wikipedia	Methylphenidate
DrugBank	Methylphenidate

Expert Committee recommendation

The Expert Committee acknowledged that attention-deficit hyperactivity disorder (ADHD) has a substantial prevalence in children and adolescents globally, and was associated with substantial disability, including reduced quality of life, poorer educational attainment, higher unemployment, increased risk of injury and higher mortality. The Committee also recognized that ADHD was also associated with increased economic burden for patients, caregivers and health systems. The Committee recalled the recommendation of the 2021 Expert Committee to not include methylphenidate on the Model Lists because of enduring uncertainty in the benefit-to-harm ratio for the long-term use of the medicine. The 2021 Committee also recommended that any future consideration of methylphenidate should address evidence for the effectiveness and safety of methylphenidate in the treatment of ADHD of at least 52 weeks duration; outcomes of the revision of the WHO mhGAP guidelines; and evaluation of health system capacity to provide appropriate diagnostic, non-pharmacological and pharmacological treatment and monitoring in low-resource settings. The 2025 Expert Committee appreciated the efforts of the applicants of the current application in presenting evidence and information addressing the 2021 Committee's recommendation. In consideration of the evidence presented in the current application for longer-term efficacy and safety of methylphenidate, the Committee noted that randomized trials evaluating long-term treatment (> 6 months) were few and all had some methodological limitations. Selected pharmacoepidemiologic studies presented some real-world evidence for benefit in functional outcomes, reductions in all-cause

mortality and unintentional injuries associated with long-term use of methylphenidate, however these studies also had intrinsic methodological limitations. The Committee noted in particular the findings of the 1999 Multimodal Treatment of ADHD study, in which ADHD treatment with stimulant medication (not limited only to methylphenidate) was associated with greater improvements in ADHD symptoms when compared to behavioural management over a period of 14 months, as rated by parents, teachers or independent investigators. Stimulant treatment was not associated with an increase in serious adverse events. The Committee also noted evidence identified during the review process from follow-up analyses of the Multimodal Treatment of ADHD study that showed that the magnitude of benefit of stimulant treatment compared to behavioural management seen at 14 months attenuated over time (after 2 years, 3 years, and into adulthood). The Committee noted that at longer follow-up the advantage associated with methylphenidate in symptom control was not retained when compared with other strategies, including behavioural therapy alone or community care. The Committee was unable to discern if the loss in sustained benefits was due to tolerance, less adherence, crossover between different strategies, and if the change in effectiveness was associated with characteristics of the children and adolescents or of the syndrome, such as baseline severity. With regard to long-term safety, the Committee noted mixed evidence of a potential association between methylphenidate use and effects on growth (weight and height), and potential for cardiovascular adverse effects. The Committee considered the conditional recommendation in the 2023 WHO mhGAP guidelines, based on low-certainty evidence, that methylphenidate may be considered for use in children (from 6 years) and adolescents with ADHD under clearly specified circumstances. The Committee considered that the mhGAP guidelines provide an important framework for supporting and increasing health system capacity to ensure the appropriate use of methylphenidate in children and adolescents. The Committee noted that the guidelines highlight, amongst other things, the limited evidence on efficacy and tolerability of methylphenidate beyond 12 weeks of treatment, that specialist reassessment of the patient's ADHD management plan should occur at least once per year, and the need for methylphenidate treatment to be offered only in the context of a comprehensive management plan. The Committee expressed concern regarding the current capacity of some health systems to ensure appropriate diagnosis, treatment (both pharmacological and non-pharmacological), and management of ADHD, particularly in low- and middle-income settings, where reported rates of mental health workers for children and adolescents are low, and among whom specialist psychiatrists are a small minority. The Committee acknowledged that methylphenidate is widely recommended and used in many countries as the standard of care for children and adolescents with ADHD and has wide regulatory approval and market availability. Furthermore, it is already included in the national essential medicines lists of some countries. The Expert Committee emphasized the need for countries listing methylphenidate to ensure that that is used within the context of comprehensive ADHD diagnosis, management and treatment services, initiated and overseen by a specialist, and only following inadequate response to recommended first-line, non-pharmacological interventions. Based on these considerations, the Expert Committee did not recommend the inclusion of methylphenidate on the EML and EMLc for the treatment of children and adolescents with ADHD because of limitations in the available evidence of benefits and safety of long-term use, which reduced confidence in the estimates of prolonged beneficial effect. The Committee further emphasized the critical need for funding and conducting rigorous research on methylphenidate and other stimulant medications. Future studies should prioritize large-scale, active placebo-RCTs with extended follow-up periods exceeding 52 weeks to adequately assess long-term efficacy and safety. While research in both adults and younger populations is important, the Committee highlighted that children and adolescents should be prioritized, as they are less able to independently evaluate treatment needs and perceived benefits compared to adults, who can make more informed choices weighing benefits against harms. The use of an active placebo is essential to maintain blinding, which is fundamental for unbiased results in RCTs, particularly when outcomes rely on psychometric scales or observer ratings. This is because methylphenidate and other stimulants often produce immediate and noticeable effects—such as mild euphoria, reduced appetite, insomnia, headache, or anxiety—that can reveal treatment allocation and artificially inflate estimates of both benefits and adverse effects when compared to inactive placebos.

Background

An application for the addition of methylphenidate to the EML and EMLc for the treatment of ADHD was considered by the Expert Committee in 2019. Listing was not recommended due to concerns about the quality and interpretation of the evidence for benefits and harms (1). Another application for methylphenidate was considered by the Expert Committee in 2021. The Committee considered new evidence presented in the application from a 2018 network meta-analysis of trials evaluating the comparative efficacy and tolerability of medicines for ADHD, including, but not limited to, methylphenidate, in children, adolescents and adults (2). The Committee noted that most of the studies included in the network meta-analysis were judged to have an unclear or high risk of bias. In addition, few of the studies measured outcomes beyond 12 weeks of treatment, which the Committee considered was

a major limitation, given that ADHD is a longer-term condition (3). Regarding safety and harms, the network meta-analysis reported on the outcome of tolerability, defined as the proportion of patients who dropped out of studies due to adverse effects. The Committee considered that this outcome did not provide adequate information on the frequency and severity of specific adverse effects associated with methylphenidate use (3). The Committee also considered that the true prevalence of ADHD was uncertain, because of variability in diagnostic approaches and the potential clinical overlap with other psychiatric illnesses. With the potential for both under- and over-diagnosis, it was therefore difficult to estimate the actual burden of disease (3). The Committee noted that the 2016 WHO Mental Health Gap Action Programme (mhGAP) guidelines recommended that the use of stimulant medication must always be part of a comprehensive treatment plan that includes psychological, behavioural and educational interventions. Recommended first-line interventions for ADHD in the WHO mhGAP guidelines are non-pharmacological (environmental, behavioural and psychosocial). Referral to a specialist for consideration of methylphenidate is only recommended after non-pharmacological interventions have failed and the child is at least 6 years old. The Committee recognized that the availability of these recommended first-line interventions and specialists in the diagnosis and treatment of children with ADHD may be limited in many low- and middle-income countries. The Committee also noted advice from the WHO Department of Mental Health and Substance Use that the mhGAP guidelines were in the process of being reviewed at that time. It was noted that the review process would take into consideration health-system capacity to: enforce and implement protocols for ADHD diagnosis; regulate the prescription and initiation of methylphenidate treatment; and ensure careful clinical monitoring of adverse effects, clinical response, adherence, treatment acceptability, requirements for dose adjustment, and risk of misuse, overmedicalization and overtreatment of behavioural problems in children (3). The Committee also noted with concern the high prevalence of non-medical use and diversion of prescription stimulants, including methylphenidate. The Committee noted that methylphenidate is included in the list of psychotropic substances under international control. As such, methylphenidate is subject to import and export restrictions and other legal mechanisms aimed at limiting its use only for scientific and medical purposes to prevent diversion and misuse (3). Overall, the Committee considered that even with the new evidence presented in the application, together with previously considered data, the benefit-to-harm ratio for the long-term use of methylphenidate remained uncertain. The Committee therefore did not recommend the inclusion of methylphenidate on the EML and EMLc. The Committee advised that for any future consideration for the listing of methylphenidate, the following would be informative: evidence for the effectiveness and safety of methylphenidate in the treatment of ADHD of at least 52 weeks duration; outcomes of the revision of the WHO mhGAP guidelines; and evaluation of health-system capacity to provide appropriate diagnostic, non-pharmacological and pharmacological treatment and monitoring in resource-constrained settings (3).

Public health relevance

According to the 2021 Global Burden of Disease study, the estimated prevalence of ADHD in people aged 20 years or younger was 1.95% (uncertainty interval (UI) 1.34% to 2.78%), corresponding to almost 47 million (UI 32 million to 67 million) people. Prevalence data showed variation across WHO regions (from 0.87% in the African region to 3.74% in the Western Pacific region), and across country income levels (from 0.97% in low-income countries to 3.54% in upper-middle-income countries. Globally, in people younger than 20 years, ADHD was associated with almost 600 000 years lived with disability (4). A diagnosis of childhood ADHD has been associated with impairment of quality of life, worse educational attainment, unemployment, criminality, increased risk of physical injuries and higher mortality (5–10). ADHD has also been associated with increased economic burden, with children diagnosed with ADHD being associated with higher costs than non-diagnosed counterparts from a societal perspective (11). ADHD is a chronic condition that has variable courses during child development. Rates of persistence of the diagnosis from childhood and adolescence into early adulthood have been reported to be around 50% (12). For many children and adolescents with ADHD, symptoms may vary with age, leading to periods of remission and recurrence (13, 14). Thus, repeated assessments over time to assess the need for continued treatment are important.

Benefits

The application presented a summary of the literature search performed and relevant evidence identified. The applicants prioritized evidence from systematic reviews and meta-analyses. Where these were unavailable, evidence from single randomized controlled trials and non-randomized and/or observational studies were presented. Studies published from 2022 onwards were highlighted, as earlier evidence had been presented in previous applications. Long-term efficacy and effectiveness Randomized controlled trials with treatment duration longer than 6 months The 1999 Multimodal Treatment of ADHD study was a four-group, parallel-design randomized controlled trial in which 579 children with ADHD aged 7 to 9.9 years were randomized to receive

medication management (n = 144), behavioural treatment (n = 144), combined treatment (n = 145) or community care (n =146) for a period of 14 months (15). Of the 289 participants randomized to medication management (alone or in combination with behavioural treatment), 212 (73.4%) remained on methylphenidate for 14 months, with an additional 39 (13.5%) switching per protocol to another medication (mostly dextroamphetamine). Intention-to-treat analyses found that at 14 months participants on combined treatment experienced a greater decrease in: teacher-ratings of inattention (standardized mean difference (SMD) −0.45, 95% confidence interval (CI) −0.7 to −0.2); parent-ratings of inattention (SMD −0.57, 95% CI −0.81 to −0.320); 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 with those receiving behavioural treatment alone. Combined treatment did not outperform behavioural treatment on teacher ratings of hyperactivity–impulsivity and aggression, classroom observer ratings of hyperactivity–impulsivity and aggression. By treatment endpoint, methylphenidate was administered at a mean daily dose of 31.2 mg in the combined treatment arm versus 37.7 mg in the medication arm. The largest treatment effects emerged during the first 50–100 days and were maintained until the study endpoint. The application highlighted the following caveats to the results of this study. First, only around 73% of participants randomized to methylphenidate were maintained on this medication at the study endpoint, when recommendations for post-study care were made, with the remaining participants being switched (within study protocol) to other pharmacological or non-pharmacological interventions. This has an impact on the conclusions about methylphenidate specifically. Second, the 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 intervention in this treatment arm may be due to non-specific effects of frequent doctor visits. Third, knowledge of the intervention may have influenced the outcome assessment. Secondary analysis of data from the 14-month Multimodal Treatment of ADHD study evaluated the effectiveness of stimulant medication in treating irritability in children with ADHD (16). The results indicated that medication management was superior to behavioural management but did not differ from community care for reducing irritability. A randomized trial in Mexico compared the efficacy of omega-3/6 fatty acids, methylphenidate, or a combination of the two, for 12 months in 90 children aged 6 to 12 years with ADHD (17). Methylphenidate was administered in a flexible-dose design with mean dose of 0.8 mg/kg a day. In the intention-to-treat analyses, children taking combination treatment showed more improvement in ADHD symptoms reported by parents (SMD −0.51, 95% CI −1.03 to 0.00) compared with those only taking omega-3/6. Treatment effects of methylphenidate were seen initially in the first 3 months and then maintained throughout the follow-up until 12 months. Limitations of the study included lack of blinding, lack of statistical power and different rates of discontinuation across arms due to the health status of participants, which may contribute to bias. Specifically, 7% of children receiving combination therapy and 20% of those receiving omega-3/6 withdrew from the study due to adverse events or no efficacy. Other randomized controlled trials A 2019 randomized, double-blind, placebo-controlled discontinuation study evaluated the continued effects of methylphenidate in 94 children and adolescents aged 8 to 18 years who had received methylphenidate treatment for more than 2 years (18). Participants were randomly assigned to continued treatment for 7 weeks with extended-release methylphenidate or gradual withdrawal over 3 weeks to 4 weeks of placebo. The primary outcome measure was investigator-rated ADHD rating scale total score. Secondary outcomes included investigator-rated Clinical Global Impressions Improvement Scale scores and the Conners' Teacher Rating Scale-Revised: Short Form score. From baseline to 7 weeks, significant differences were seen between discontinuation and continuation groups favouring the continuation group for ADHD rating scale total scores (mean difference (MD) −4.6, 95% CI −8.7 to −0.6), and Conners' Teacher Rating Scale ADHD index scores (MD −6.6, 95% CI −9.5 to −3.7). Investigator-rated worsening in overall functioning was reported for 40.4% and 15.9% of participants in the discontinuation and continuation arms, respectively. Other studies incorporating randomized discontinuation of methylphenidate have also reported an overall worsening of symptoms after discontinuation (19). The length of time that children had been on methylphenidate varied considerably between studies (from 1 year to 1 week). Additionally, in most studies, a minority of children and adolescents with ADHD did not relapse or deteriorate when taken off medications for ADHD. The findings are limited by features such as participants perhaps being functionally unblinded due to subject-perceived effects of stopping the medicine. Observational studies An observational nationwide cohort study in Sweden evaluated individuals aged 6 to 64 years with an incident diagnosis of ADHD between 2007 and 2018, who were medication naive before diagnosis (20). Individuals were followed up from diagnosis until either death, emigration, 2 years after ADHD diagnosis or until the study end date of 31 December 2020. Outcomes assessed were all-cause mortality, natural-cause and unnatural-cause mortality. Among 145 578 individuals with ADHD, 84 204 started medication for the condition. The median age at diagnosis was 17.4 years. A significantly lower rate was found favouring the initiation group of all-cause mortality (risk difference (RD) −8.9 per 10 000, 95% CI −17.3 to −0.6; hazard ratio (HR) 0.79, 95% CI 0.70 to 0.88), and unnatural-cause mortality (RD −7.4 per 10 000, 95% CI −14.2 to −0.5; HR 0.75, 95% CI 0.66 to 0.86) during the 2-year follow-up period. No significant difference was seen between groups for natural cause mortality (RD −1.6

per 10 000, 95% CI −6.4 to 3.2; HR 0.86, 95% CI, 0.71 to 1.05). In subgroup analyses, a significant association with lower rates of all-cause and unnatural-cause mortality was also observed for individuals aged 6 to 24 years. A population-based retrospective cohort study in Canada assessed the association between ADHD medication use and the risk of all-cause mortality and unintentional injuries leading to emergency department or hospital admission in 217 192 individuals aged ≤ 24 years with ADHD between 2000 and 2021 (21). Episodes of ADHD medication use were associated with reduced risk of all-cause mortality (adjusted HR 0.61, 95% CI 0.48 to 0.76), unintentional injuries leading to hospitalization (adjusted HR 0.71, 95% CI 0.68 to 0.75) and unintentional injuries leading to emergency department visits (adjusted HR 0.75, 95% CI 0.74 to 0.77). Systematic reviews A 2020 systematic review and meta-analysis evaluated the effects of ADHD medications on functional outcomes using literature from large population-based databases and registries published before January 2019 (22). The review included 40 articles in a qualitative review, of which 21 were suitable for quantitative meta-analysis. Pooled results of the meta-analysis found that ADHD patients taking stimulants and/or non-stimulants had significantly decreased odds of developing mood disorders (odds ratio (OR) 0.80, 95% CI 0.76 to 1.84), accidents and injuries (OR 0.72, 95% CI 0.59 to 0.87) and poor academic outcomes (OR 0.80, 95% CI 0.76 to 0.84). For outcomes of suicidality, substance use disorders, criminality and traumatic brain injury, risks were reduced but were not statistically significant. Short-term efficacy Methylphenidate versus placebo/no treatment A 2023 Cochrane systematic review of 212 randomized controlled trials (16 302 participants) evaluated the benefits and harms of methylphenidate versus placebo or no treatment in children and adolescents aged 18 years and younger with ADHD (23). Most trials were conducted in high-income countries and about 40% were fully or partly industry funded. The mean age of participants was 9.8 years and the mean duration of treatment across all trials was 28.8 days. This review was an update of the review conducted in 2015 of 185 randomized controlled trials (12 245 participants) which had been presented in previous applications for methylphenidate (24). Compared with placebo or no treatment, the updated review found very-low-certainty evidence that methylphenidate may improve teacher-rated ADHD symptoms (SMD −0.74, 95% CI −0.88 to −0.61; 21 randomized controlled trials, 1728 participants), corresponding to a mean difference of −10.58 points (95% CI −12.58 to −8.72) on the ADHD rating scale (a change of 6.6 points on this scale is considered the minimal clinically relevant difference). The quality of evidence was downgraded two levels due to high risk of bias, and one level due to moderate statistical heterogeneity. In a subgroup analysis of trials at low and high risk of bias, no evidence was found that the risk of bias influenced the effect estimate. For the outcome of independent assessor-rated ADHD symptoms, evidence of benefit was found favouring methylphenidate (SMD −1.10, 95% CI −1.44 to −0.77; 22 randomized controlled trials, 3724 participants), corresponding to an MD of −15.7 points (95% CI −14.7 to −7.9) on the ADHD rating scale. When two trials considered outliers with unrealistically high effect sizes were removed, the SMD was −−0.62, 95% CI −0.79 to −0.46, corresponding to a mean difference of −8.7 points on the ADHD rating scale. In a subgroup analysis of trials at low and high risk of bias, the benefit of methylphenidate was lower in trials with low risk (SMD −0.40, 95% CI −0.78 to −0.03; four randomized controlled trials, 942 participants) than in those with high risk (SMD −1.30, 95% CI −1.70 to −0.89; I^2 = 96%; 18 trials, 2782 participants). The mean difference in ADHD rating scale scores from trials with low risk of bias (one randomized controlled trial, 253 participants) was −5.7 points (95% CI −10.4 to −0.4) and below the minimal clinically relevant difference. Another subgroup analysis found lower effects of methylphenidate in long-term trials (SMD −0.35, 95% CI 0.61 to −0.08; one randomized controlled trial, 221 participants) than in short-term trials (SMD −1.15, 95% CI −1.50 to −0.80; 21 randomized controlled trials, 3503 participants). The mean difference in ADHD rating scale scores from long-term trials was −5.0 points (95% CI −8.7 to −1.1) and below the minimal clinically relevant difference (23). For the outcome of parent-rated ADHD symptoms, evidence was found of benefit favouring methylphenidate (SMD −0.63, 95% CI −0.76 to −0.50; 27 randomized controlled trials, 2927 participants), corresponding to a mean difference of −9.0 points on the ADHD rating scale. In a subgroup analysis of trials at low and high risk of bias, no evidence was found that risk of bias influenced the estimate of effect (23). The application presented issues raised by researchers about the ratings of the certainty of evidence from the Cochrane. They were considered to be overly stringent in downgrading the quality of evidence due to risk of bias and heterogeneity. There is debate about: the extent to which lack of blinding contributes to exaggerated comparative treatment effects for subjective outcomes; that the lack of differences between randomized controlled trials at different risk of bias could indicate a functional unblinding due to adverse events; and the different measures of heterogeneity (tau2 and I2) producing different outcomes. A 2022 meta-analysis of 31 studies (804 participants) evaluated dose-dependent effects of methylphenidate on neurocognitive functions in children and adolescents aged 5–18 years with ADHD (25). Duration of methylphenidate treatment ranged from 1 to 21 days. All the studies included were rated as having a low risk of bias. Outcomes assessed included variability in baseline response speed, non-executive memory and executive memory, inhibitory control, and cognitive flexibility. ADHD symptoms were assessed if available. Methylphenidate was reported to have beneficial effects on all neurocognitive functions assessed, with SMDs for effect sizes ranging from 0.20 (95% CI 0.03 to 0.38) for

executive memory to 0.73 (95% CI 0.60 to 0.85) for variability in responding. Methylphenidate was associated with benefit in terms of aggregated parent and teacher symptom rating scales (SMD 0.95, 95% CI 0.78 to 1.14). Significant linear dosing effects were found for ADHD symptoms, baseline speed, variability in responding and non-executive memory. No dosing effects were found for executive memory, inhibitory control or cognitive flexibility. A 2018 systematic review and meta-analysis of 34 studies (1777 participants) evaluated the effects of methylphenidate compared with placebo on academic productivity and accuracy in children with ADHD (26). Outcomes significantly favoured methylphenidate for: math accuracy (RD 3%, 95% CI 1.2% to 4.8%; 29 studies, 1528 participants); math productivity (RD 7.8%, 95% CI 4.3% to 11.2%; 17 studies, 912 participants); and number of reading items attempted (SMD 0.47, 95% CI 0.30 to 0.64; five studies, 100 participants). For reading accuracy, a non-significant treatment effect was observed favouring methylphenidate (RD 6.2%, 95% CI −0.9% to 13.4%; nine studies, 207 participants). No evidence of heterogeneity or publication bias was observed. Of note, these results were based on studies of short duration (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. Comparison with other medications for ADHD A 2018 systematic review and network meta-analysis evaluated the comparative efficacy and tolerability of pharmacological interventions for ADHD, including methylphenidate, versus each other or placebo (2). The review included 133 randomized controlled trials, including 81 (14 346 participants) in children and adolescents aged 5–17 years. The efficacy analysis was based on 10 068 children and adolescents. In head-to-head comparisons, for the outcome of ADHD core symptoms rated by clinicians closest to 12 weeks, methylphenidate was superior to atomoxetine (SMD −0.22, 95% CI −0.39 to −0.05; low-quality), but inferior to amphetamines (SMD 0.24, 95% CI 0.05 to 0.44; low-quality evidence. No significant differences were seen between methylphenidate and: bupropion (SMD −0.18, 95% CI −0.9 to 0.54, very-low-quality evidence); clonidine (SMD 0.07, 95% CI −0.42 to 0.56; very-low-quality evidence); and guanfacine (SMD 0.11, 95% CI −0.13 to 0.34; low-quality evidence). For ADHD core symptoms rated by teachers, no differences were seen between methylphenidate and atomoxetine, bupropion or guanfacine. For tolerability, measured as the proportion of participants who discontinued treatment due to adverse events, amphetamines and guanfacine were significantly inferior to placebo. No significant differences were seen between other pharmacological interventions and placebo for this outcome.

Harms

In response to the concerns raised by the previous Expert Committee, the application focused on adverse events that occur in the longer term with methylphenidate. Long-term safety In the above-mentioned randomized controlled trials of long-term methylphenidate treatment (15, 17) and an observational study of long-term safety of methylphenidate treatment (ADDUCE) (27), no association was found between methylphenidate treatment and serious adverse events. Effects on growth A 2021 systematic review and meta-analysis of 18 observational studies (4868 participants) evaluated the association between long-term (> 6 months) methylphenidate treatment and growth (28). The average daily dosage of methylphenidate across studies was about 30 mg. The meta-analyses indicated statistically significant pre–post differences in 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 about 1.39 cm and of weight gain by about 1.96 kg for a 10-year-old boy over a 2-year period. The most prominent effects on weight were seen in the first 12 months of treatment, and on height within the first 24–30 months. A 2020 study estimated the long-term associations of stimulant medication on growth trajectories from childhood to adulthood in the Multimodal Treatment of ADHD study (29). Over a period of 16 years, 568 children with ADHD and 258 controls were assessed eight times. The study found that children consistently treated with methylphenidate and other stimulants from ages 7–9.9 years through to adolescence were on average 4.06 cm shorter by mean age 24.7 years than children who were not treated and 2.74 cm shorter than children who were inconsistently treated across the same period. The ADDUCE study was a naturalistic, longitudinal, controlled study that evaluated the long-term safety of methylphenidate in 1410 children and adolescents aged 6–17 years with ADHD in 27 European child and adolescent mental health centres (27). Participants were recruited into three cohorts: medication-naive ADHD patients who intended to start methylphenidate treatment (methylphenidate group, n = 756), medication-naive ADHD patients who did not intend to start any ADHD medication (no-methylphenidate group, n = 391) and a control group without ADHD (n = 263). The study found no difference in height velocity at any time point between the methylphenidate and no-methylphenidate groups. A slowing in weight velocity was observed in the methylphenidate group only at the 6-month time point. No differences between groups were observed for body mass index. Cardiovascular safety A 2012 study estimated the long-term associations of stimulant medication on blood pressure and heart rate in the Multimodal Treatment of ADHD study (30). At the study endpoint (14 months), children who received combined treatment had a significantly higher heart rate than those treated with behavioural therapy alone (mean (standard

deviation) 84.6 (12.2) versus 79.1 (12.0); P = 0.01). No difference was observed thereafter. No treatment effects were observed on systolic or diastolic blood pressure. A 2022 systematic review and meta-analysis of 19 observational studies (3 931 532 participants, including children, adolescents and adults) evaluated possible associations between ADHD medications (including methylphenidate) and the risk of a range of cardiovascular events (31). Fourteen of the studies were cohort studies and the median follow-up time was 1.5 years (range 0.25 to 9.5 years). ADHD medication use was not significantly associated with an increased risk of any cardiovascular events in children and adolescents (pooled adjusted relative risk (RR) 1.18, 95% CI 0.91 to 1.53) or in older age cohorts. The ADDUCE study 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 (27). A 2023 Swedish register-based case–control study evaluated the long-term risk of cardiovascular diseases associated with ADHD medications (including methylphenidate) in 278 027 individuals aged 6 to 64 years (32). A total of 10 388 individuals with ADHD who had a cardiovascular event were demographically matched with 51 672 controls with ADHD and without a cardiovascular event. Both groups had a median follow-up period of 4.1 years. Methylphenidate was the dispensed medication in 76.2% and 76.1% of cases and controls, respectively. The study found evidence for an increased risk of cardiovascular disease with longer cumulative duration of ADHD medication use compared with non-use, for example, at 0 to ≤ 1 year (adjusted OR 0.99, 95% CI 0.93 to 1.06) and at > 5 years (adjusted OR 1.23, 95% CI 1.12 to 1.36). Longer cumulative duration of ADHD medication was also associated with a significantly increased risk of hypertension and arterial disease, but not arrhythmia, heart failure, ischaemic heart disease, thromboembolic disease or cerebrovascular disease. A 2024 Swedish retrospective, population-based cohort study investigated the association between cardiovascular events and short-term methylphenidate use in 252 382 participants aged 12 to 60 years with ADHD (33). Rates of cardiovascular events were compared 1 year before methylphenidate treatment and 6 months after starting methylphenidate treatment. The posterior probabilities of at least a 10% increased risk of cardiovascular events were 70% and 49% for methylphenidate and control groups, respectively. The probability of finding a methylphenidate-related difference in risk decreased when considering risk levels of 20% or larger. This study did not consider children younger than 12 years and lacked data on dosage effects (which have emerged as important factors in other studies of cardiovascular risk). Psychiatric/neurological adverse events In the ADDUCE study, the prevalence of suicidality (ideation or behaviour) decreased for all groups from baseline to 24 months to 3.17%, 0.77% and 0.76% in the methylphenidate, no-methylphenidate and control groups, respectively. No significant between-group differences were seen after adjusting for baseline differences. Parent- and child-ratings of mood improved in those taking methylphenidate compared with the no methylphenidate group from baseline to 24 months. The prevalence of psychotic-like symptoms decreased from baseline to 24 months, with no significant difference between groups (27). Short-term safety The application also presented a summary of evidence for the safety of methylphenidate from short-term treatment studies. Non-medical use and diversion A 2020 systematic review of 111 studies evaluated the non-medical use and diversion of prescription stimulants (34). Of the studies included, 86 addressed the epidemiology of non-medical use and diversion. Rates of these behaviours varied widely across studies and generally focused on older adolescents and young adults. The prevalence rates of non-medical use ranged from 2.1% to 58.7% and diversion rates from 0.7% to 80.0%. Academic and occupational performance enhancement were the most commonly cited motivations. The 2018 College Prescription Study was a multi-institutional survey of the non-medical use of prescription medicines in 19 539 undergraduate and graduate students and those in professional programmes in the United States (35). Among respondents, 9.1%, 9.4% and 15.9% reported non-medical use of pain medications, sedatives and stimulants, respectively. Of these, 44.6%, 57.9% and 62.9% reported non-medical use of pain medications, sedatives and stimulants, respectively in the previous 12 months. Among non-medical users of stimulants, 47% reported use 1–9 times in the previous 12 months. A 2023 cross-sectional study used survey data to estimate the prevalence and association between stimulant therapy for ADHD and non-medical use in United States secondary-school students (36). From datasets collected across 3284 schools between 2005 and 2020, among 231 141 students, the mean prevalence of non-medical use of prescription stimulants in the past year was 5.7% at the school level and 6.0% at the individual level. Different variables were associated with non-medical use, for example, other substance use such as marijuana and alcohol, parental college education, greater percentage of student body identifying as white and greater percentage of student body using prescribed stimulant medications). A 2023 survey study of drug use in United States secondary school students found the prevalence of non-medical use of methylphenidate declined from 2001 to 2021: from 2.9% to 0.6% of eighth graders, 4.8% to 0.5% of 10th graders and from 5.1% to 0.6% of 12th graders (37). Most non-medical stimulant use has been associated with no, or minor, medical effects. However serious adverse events can occur, particularly when administered by non-oral routes for example, injection or nasal inhalation (38). Methylphenidate is a controlled substance in many countries and its prescribing and dispensing are subject to regulatory

restrictions that aim to minimize non-medical use and diversion including: • special training and licensing requirements for prescribing; • monitoring of prescription rates by regulatory authorities to flag excessively high, unexplained rates of prescription; • inability to issue refill prescriptions; • requirement for regular monitoring and ongoing assessments of the need for the medication; • prescription of formulations that may have less potential for non-medical use. Additionally, many other strategies have been offered in the clinical and research literature, by government agencies and professional organizations, in studies testing reduction of non-medical use and diversion (e.g. use of extended-release instead of immediate-release formulations) (34, 39–41) and in studies testing training programmes for physicians designed to help them prevent or reduce stimulant diversion and misuse (42, 43). Risk of later substance use after stimulant treatment The Multimodal Treatment of ADHD study and other observational studies indicate that there is no evidence of an association between methylphenidate use in children with ADHD and an increased risk for substance use in adolescents and young adults (44–46). Large epidemiological studies have found protective effects for substance use outcomes of medications for ADHD in which within-subject analyses have compared medicated and unmedicated periods, allowing control for confounding by indication (46). For example, in an analysis of commercial health-care claims in the United States between 2004 and 2014 for more than 2.9 million adolescents and adults with ADHD, male and female patients had 35% and 31%, respectively, lower odds of concurrent referrals to emergency departments for substance-related events when receiving medication (47). Data on the progression to misuse among young people prescribed stimulants from the Monitoring the Future study found that initiation of stimulant treatment for ADHD in childhood was not associated with an elevated risk of substance use, defined as cocaine, methamphetamine or prescription stimulant misuse in adolescence. However, start of stimulant treatment at older ages (≥ 10 years) and for shorter duration was associated with higher odds of past-year cocaine or prescription stimulant misuse in adolescence than those starting treatment in childhood. However, causal relationships could not be concluded based on the methodology (self-reported survey, retrospective data). In addition, it is not possible to account for confounders that might drive late initiation of treatment.

Cost / cost effectiveness

The application presented prices of methylphenidate 10 mg tablets in different countries. The prices per unit (tablet) ranged from 0.03 United States dollars (US$) in Viet Nam to US$ 0.90 in Malaysia. No price information was presented for the other strengths or for the extended-release formulations of methylphenidate also proposed for inclusion on the Model Lists. The application noted that costs may vary depending on the formulation, manufacturer or both. No new evidence of cost–effectiveness were presented, beyond that already considered by the Expert Committee in previous applications. In 2019, the Expert Committee acknowledged that methylphenidate appeared to be low cost and affordable, but considered that no conclusions could be drawn on the cost–effectiveness of the medicine given the considerable uncertainty in the estimates of benefits and harms (1).

WHO guidelines

The 2023 WHO mhGAP guideline for mental, neurological and substance use disorders includes the following conditional recommendation (low-certainty evidence) for methylphenidate in the treatment of ADHD (48). For children 6 years old and older and adolescents who have an attention deficit hyperactivity disorder (ADHD) diagnosis, methylphenidate may be considered, provided: • ADHD symptoms are still causing persistent significant impairment in at least one domain of functioning (education, interpersonal relationships, occupation), after the implementation of environmental modifications in schools, at home or in other relevant settings; • a careful assessment of the child/adolescent has been conducted; • 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 guideline highlights the following remarks with regard to methylphenidate treatment. • Treatment 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. • Treatment should be combined when possible with brief parent behavioural therapies. • Children and adolescents receiving treatment should be maintained under close clinical monitoring for improvement in symptoms and prevention of adverse effects. • A specialist care provider trained in management of ADHD should reassess the child/adolescent's management plan for ADHD at least once a year. • The rationale for specialist assessment before prescription of methylphenidate is that diagnosis of ADHD requires specialist clinical judgement especially given the risks of misuse. The guideline also includes specific considerations with regard to research gaps and implementation considerations. • Strengthened intervention designs are needed with long-term follow-up to ascertain lasting intervention benefits, harms and acceptability in children and adolescents. • More evidence needs to be made available on protocol adherence, misuse/safety, and treatment satisfaction when

treatment with methylphenidate is prescribed and monitored in primary health-care settings. • It is Important to consider the health system's capacity to enforce and implement protocols for ADHD diagnosis.

Availability

The application reported that methylphenidate is approved in over 70 jurisdictions globally and is included on the national essential medicines lists of more than 50 countries.

Other considerations

The Department of Mental Health, Brain Health and Substance Use reviewed the application. The technical department referred to the recommendation on methylphenidate treatment in older children and adolescents with ADHD in the 2023 mhGAP guidelines and highlighted remarks made by the guideline group.

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