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	Multiple formulations and strengths.
EML status history	Application rejected in 2019 (TRS 1021) Application rejected in 2021 (TRS 1035)
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 recalled the decision by the 2019 Expert Committee not to recommend methylphenidate for inclusion on the EML and EMLc for the treatment of ADHD due to concerns about the quality and interpretation of the evidence presented on benefits and harms. The Committee considered the new evidence in the current application from a 2018 network meta-analysis of trials evaluating the comparative efficacy and tolerability of medications for ADHD, including but not limited to methylphenidate, in children, adolescents and adults. The Committee noted that most of the included studies in the network meta-analysis were judged to have an unclear or high risk of bias. In addition, few of the included studies measured outcomes beyond 12 weeks of treatment, which the Committee considered was a major limitation, given that ADHD is a longer-term condition. With regard to safety and harms, the network meta-analysis reported on the outcome of tolerability, defined as the proportion of patients who dropped out of studies because of 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. Known adverse effects of methylphenidate that require monitoring include effects on height velocity and weight, and cardiovascular effects such as changes in heart rate and blood pressure. 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. Given the potential for both under- and over-diagnosis, it is therefore difficult to estimate the actual burden of disease. The Committee noted that the 2016 WHO 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 are currently in the process of being reviewed and that the review process will take into consideration health systems 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. 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. 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 was still 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 low-resource settings.

Background

An application for the inclusion of methylphenidate on 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).

Public health relevance

In 2019, the global prevalence of ADHD was estimated to be 2.6% of children and adolescents aged 5 to 19 years; within this age group, ADHD accounted for 0.29% of total global disability-adjusted life years (DALYs) (2). Studies and meta-analyses have shown ADHD to be associated impairment of quality of life (3,4), social and emotional impairment (5–8), greater risk of accidental injuries (9–15), greater risk of premature death and suicide (16–21), increased crime and delinquency (22–26), educational underachievement (27–29), substance use disorders (30–32) and increased economic burden for individuals, families and society (33–42).

Benefits

The current application represented much of the same evidence included in the 2019 application. The new evidence included in the current application is summarized below. Evidence for short-term efficacy from randomized controlled trials A 2018 systematic review and network meta-analysis evaluated the comparative efficacy of oral medications for ADHD, including methylphenidate, versus each other or placebo (43). It comprised 133 randomized controlled trials, including 81 trials in children and adolescents, 51 in adults and one in both. A total of 14 346 children and adolescents were included in the efficacy analysis. The overall risk of bias was rated as low in 23.5% of the studies included, unclear in 65.4%, and high in 11.1%. The primary efficacy outcome was measured as change in severity of ADHD core symptoms based on teachers' and clinicians' ratings, at time points closest to 12 weeks of treatment. In children and adolescents, methylphenidate was superior to placebo with respect to ADHD core symptoms rated by both clinicians (standard mean difference (SMD) –0.78, 95% CI –0.93 to –0.62) and teachers (SMD –0.82, 95% CI –1.16 to –0.37). The quality of the evidence from randomized controlled trials in children and adolescents for the comparison of methylphenidate versus placebo was rated as low for teachers' ratings (five studies) and moderate for clinicians' ratings (five studies). Evidence for longer-term effectiveness from observational studies A qualitative systematic review of 40 observational studies from 2008 to 2019 investigated the effects of ADHD medication on behavioural and neuropsychiatric outcomes using linked prescription databases. It included 18 studies that used within-individual designs to account for confounding by indication (44). These studies found short-term beneficial effects of ADHD medication (not limited to methylphenidate) for outcomes such as injuries, motor vehicle accidents, substance use disorder and education, with estimates of relative reduction ranging from 9% to 58%. The within-

individual studies found no evidence of increased risks of suicidality and seizures. Most of the within-individual studies included in the systematic review were short-term studies. The authors concluded that the available evidence from pharmacoepidemiological studies on long-term effects of ADHD medication were less clear.

Harms

The most common adverse effects of methylphenidate are loss of appetite and insomnia. Other common adverse effects include erythema, headache, mild labile mood, nasal congestion, nasopharyngitis, nausea, vomiting and weight loss (45–48). A 2018 systematic review and network meta-analysis evaluated the tolerability of medications, including methylphenidate, for ADHD in children, adolescents and adults (43). Tolerability was measured as the proportion of patients who dropped out of studies because of side-effects. The review included 82 trials (11 018 children and adolescents) in the tolerability analysis. The tolerability of methylphenidate was not significantly different from placebo (odds ratio (OR) 1.44, 95% CI 0.90 to 2.31). In children and adolescents, compared with placebo, the use of methylphenidate was associated with significantly increased diastolic blood pressure (SMD 0.24, 95% CI 0.14 to 0.33) and decreased weight (SMD –0.77, 95% CI –1.09 to –0.45). There was no significant increase in systolic blood pressure (SMD 0.09, 95% CI –0.01 to 0.19). A 2015 Cochrane systematic review of randomized clinical trials of methylphenidate in children and adolescents with ADHD found no increase in serious adverse events, but a high proportion of participants suffered a range of non-serious adverse events (49). A 2018 Cochrane systematic review of 260 non-randomized studies evaluated adverse events of methylphenidate in children and adolescents with ADHD (50). Among other findings, the review found very low quality evidence that methylphenidate increased the risk of serious adverse events (risk ratio (RR) 1.36, 95% CI 1.17 to 1.57; two studies, 72 005 participants); any psychotic disorder (RR 1.36, 95% CI 1.17 to 1.57; one study, 71 771 participants); and arrhythmia (RR 1.61, 95% CI 1.48 to 1.74; one study, 1224 participants). In contrast, two large population-based cohort studies using within-person designs found no evidence that methylphenidate was associated with psychotic disorders (51,52). A 2020 meta-review of network meta-analyses, meta-analyses of randomized controlled trials, individual randomized controlled trials, and cohort studies reported 78 adverse effects across 80 psychotropic medications in 337 686 children and adolescents with mental disorders (53). It reported that, compared with placebo, methylphenidate was associated with significantly worse anorexia (RR 3.21, 95% CI 2.61 to 3.94), insomnia (OR 4.66, 95% CI 1.99 to 10.9), weight loss (SMD –0.77, 95% CI –1.09 to –0.45), nausea (RR 1.38, 95% CI 1.04 to 1.84) and abdominal pain (RR 1.50, CI 1.26 to 1.79). Adverse effects of methylphenidate reported in observational studies include effects on height and weight (54,55), cardiovascular events (56–58), and cardiac malformations in infants born to women treated with methylphenidate during pregnancy (59).

Cost / cost effectiveness

The current application identified no new evidence on the cost–effectiveness of methylphenidate since the 2019 application. 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 2016 WHO mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings (version 2.0) (60) makes the following recommendations for the management of ADHD. • Provide guidance on child/adolescent well-being. • Provide psychoeducation to person and carers and parenting advice. Provide guidance on improving behaviour. • Assess for and manage stressors, reduce stress and strengthen social support. • Provide carer support. • Liaise with teachers and other school staff. • Link with other available resources in the community. • Consider parent skills training when available. • Consider behavioural interventions when available. • If above treatments have failed AND the child/adolescent has a diagnosis of ADHD AND is at least 6 years old, refer to a specialist for methylphenidate treatment. • Ensure appropriate follow-up every 3 months or more, if needed.

Availability

Methylphenidate, in various formulations and strengths, is available globally in originator and generic brands.

Other considerations

Non-medical use and diversion A 2020 systematic review of the literature on the non-medical use and diversion of prescription stimulants (111 studies) found that non-medical use and diversion are highly prevalent. Self-reported rates among population samples ranged from 2.1% to 58.7% for non-medical use and from 0.7% to 80.0% for diversion. In most cases, non-medical use is associated with no, or minor, medical effects; however, adverse medical outcomes, including death, occur in some individuals, particularly when administered by non-oral routes. Methylphenidate should be used with caution or not at all in patients at risk of diversion or misuse (61). Diagnosis ADHD can only be diagnosed by a licensed clinician who interviews the parent or caregiver and/or patient to document criteria for the disorder. The condition cannot be diagnosed by rating scales alone, neuropsychological tests or methods for imaging the brain (62–68). The diagnosis requires: 1) the presence of developmentally inappropriate levels of hyperactive–impulsive and/or inattentive symptoms for at least 6 months; 2) symptoms occurring in different settings (e.g. home and school); 3) symptoms that cause impairment in living; 4) some of the symptoms and impairments first occurring in early to mid-childhood (before age 12 years); and 5) no other disorder better explains the symptoms (62,68,69). Comments on the application were provided by the WHO Department of Mental Health and Substance Use. The technical department advised that the guidelines of the Mental Health Gap Action Programme (mhGAP) include the use of methylphenidate in the management of children at least 6 years old with a diagnosis of ADHD. Methylphenidate is provided as second-line treatment (after parent training and behavioural interventions) and must be initiated by a specialist. The mhGAP guideline update process is underway and this recommendation will be examined to consider if it needs to be modified. Important considerations for the Expert Committee were highlighted relating to health systems capacity to enforce and implement protocols for ADHD diagnosis, to prescribe and initiate methylphenidate treatment, and to ensure careful clinical monitoring for side-effects, clinical response, adherence, treatment acceptability and dose adjustment. The risks of methylphenidate misuse, overmedicalization and overtreatment of behavioural problems in children will also be considered.

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