

# Methylphenidate

REFUSÉE

Le Comité d'experts, après évaluation, refuse d'inscrire le médicament proposé dans la demande.  
La Liste Modèle des Médicaments Essentiels fait état des raisons que les membres du Comité ont identifiées pour refuser l'inscription.

## Section: 24. Medicines for mental and behavioural disorders

EMLc

Codes ATC: N06BA04

Indication	Attention deficit hyperactivity disorder	Code ICD11: 6A05
INN	Methylphenidate	
Type de médicament	Chemical agent	
Type de liste	Liste complémentaire (EML) (EMLc)	
Formulations	Multiple formulations and strengths.	
Historique des statuts LME	Demande refusée en 2019 (TRS 1021) Demande refusée en 2021 (TRS 1035)	
Sexe	Tous	
Âge	Aussi recommandé pour les enfants	
Équivalence thérapeutique	La recommandation concerne ce médicament spécifique	
Renseignements sur le brevet	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 <a href="http://www.MedsPal.org">www.MedsPal.org</a> Lire la suite <a href="#">sur les brevets.</a>	
Wikipédia	<a href="#">Methylphenidate</a>	
DrugBank	<a href="#">Methylphenidate</a>	

## Recommandation du comité d'experts

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.

### Contexte

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).

### Pertinence pour la santé publique

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).

### Bénéfices

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.

## Torts

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).

## Rapport coût/efficacité

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).

## Directives de l'OMS

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.

## Disponibilité

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

## Autres considérations

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.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2019 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2019 (WHO Technical Report Series, No. 1021; <https://apps.who.int/iris/handle/10665/330668>, accessed 6 June 2021).
2. GHDx. GBD results tool. Seattle, WA: Institute for Health Metrics and Evaluation; 2021 (<http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2019-permalink/d834d7a2497b21627729eae140c39f6d>, accessed 6 June 2021).
3. Lee YC, Yang HJ, Chen VC, Lee WT, Teng MJ, Lin CH, et al. Meta-analysis of quality of life in children and adolescents with ADHD: By both parent proxy-report and child self-report using PedsQL. *Res Dev Disabil*. 2016;51–52:160–72.
4. Dey M, Paz Castro R, Haug S, Schaub MP. Quality of life of parents of mentally-ill children: a systematic review and meta-analysis. *Epidemiol Psychiatr Sci*. 2019;28(5):563–77.
5. Strine TW, Lesesne CA, Okoro CA, McGuire LC, Chapman DP, Balluz LS, et al. Emotional and behavioral difficulties and impairments in everyday functioning among children with a history of attention-deficit/hyperactivity disorder. *Prev Chronic Dis*. 2006;3(2):A52.
6. Beheshti A, Chavanon ML, Christiansen H. Emotion dysregulation in adults with attention deficit hyperactivity disorder: a meta-analysis. *BMC Psychiatry*. 2020;20(1):120.
7. Ros R, Graziano PA. Social functioning in children with or at risk for attention deficit/hyperactivity disorder: a meta-analytic review. *J Clin Child Adolesc Psychol*. 2018;47(2):213–35.
8. Benedict FT, Vivier PM, Gjelsvik A. Mental health and bullying in the United States among children aged 6 to 17 years. *J Interpers Violence*. 2015;30(5):782–95.
9. Yeh JY, Hou TY, Tseng WT, Chen VC, Yang YH, Kuo TY, et al. Association between attention deficit hyperactivity disorder and risk of burn injury: a propensity-matched cohort study. *Neuropsychiatr Dis Treat*. 2020;16:1249–55.
10. Ruiz-Goikoetxea M, Cortese S, Aznarez-Sanado M, Magallon S, Alvarez Zallo N, Luis EO, et al. Risk of unintentional injuries in children and adolescents with ADHD and the impact of ADHD medications: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2018;84:63–71.
11. Chang Z, Lichtenstein P, D'Onofrio BM, Sjolander A, Larsson H. Serious transport accidents in adults with attention-deficit/hyperactivity disorder and the effect of medication: a population-based study. *JAMA Psychiatry*. 2014;71(3):319–25.
12. Nelson LD, Guskiewicz KM, Marshall SW, Hammeke T, Barr W, Randolph C, et al. Multiple self-reported concussions are more prevalent in athletes with ADHD and learning disability. *Clin J Sport Med*. 2016;26(2):120–7.
13. Vaa T. ADHD and relative risk of accidents in road traffic: a meta-analysis. *Accid Anal Prev*. 2014;62:415–25.
14. Curry AE, Metzger KB, Pfeiffer MR, Elliott MR, Winston FK, Power TJ. Motor vehicle crash risk among adolescents and young adults with attention-deficit/hyperactivity disorder. *JAMA Pediatr*. 2017;171(8):756–63.
15. Adeyemo BO, Biederman J, Zafonte R, Kagan E, Spencer TJ, Uchida M, et al. Mild traumatic brain injury and ADHD: a systematic review of the literature and meta-analysis. *J Atten Disord*. 2014;18(7):576–84.
16. Dalsgaard S, Ostergaard SD, Leckman JF, Mortensen PB, Pedersen MG. Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study. *Lancet*. 2015;385(9983):2190–6.
17. Chen VC, Chan HL, Wu SI, Lee M, Lu ML, Liang HY, et al. Attention-deficit/hyperactivity disorder and mortality risk in Taiwan. *JAMA Netw Open*. 2019;2(8):e198714.
18. Fitzgerald C, Dalsgaard S, Nordentoft M, Erlangsen A. Suicidal behaviour among persons with attention-deficit hyperactivity disorder. *Br J Psychiatry*. 2019; 215(4):615–20.
19. Septier M, Stordeur C, Zhang J, Delorme R, Cortese S. Association between suicidal spectrum behaviors and attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2019;103:109–18.
20. Huang KL, Wei HT, Hsu JW, Bai YM, Su TP, Li CT, et al. Risk of suicide attempts in adolescents and young adults with attention-deficit hyperactivity disorder: a nationwide longitudinal study. *Br J Psychiatry*. 2018;212(4):234–8.
21. Sun S, Kuja-Halkola R, Faraone SV, D'Onofrio BM, Dalsgaard S, Chang Z, et al. Association of psychiatric comorbidity with the risk of premature death among children and adults with attention-deficit/hyperactivity disorder. *JAMA Psychiatry*. 2019;76(11):1141–9.
22. Mohr-Jensen C, Muller Bisgaard C, Boldsen SK, Steinhausen HC. Attention-deficit/hyperactivity disorder in childhood and adolescence and the risk of crime in young adulthood in a Danish nationwide study. *J Am Acad Child Adolesc Psychiatry*. 2019;58(4):443–52.
23. Young S, Moss D, Sedgwick O, Fridman M, Hodgkins P. A meta-analysis of the prevalence of attention deficit hyperactivity disorder in incarcerated populations. *Psychol Med*. 2015;45(2):247–58.

24. McCauley HL, Breslau JA, Saito N, Miller E. Psychiatric disorders prior to dating initiation and physical dating violence before age 21: findings from the National Comorbidity Survey Replication (NCS-R). *Soc Psychiatry Psychiatr Epidemiol.* 2015;50(9):1357–65.
25. Gudjonsson GH, Sigurdsson JF, Sigfusdottir ID, Asgeirsdottir BB, Gonzalez RA, Young S. A national epidemiological study investigating risk factors for police interrogation and false confession among juveniles and young persons. *Soc Psychiatry Psychiatr Epidemiol.* 2016;51(3):359–67.
26. Christoffersen MN. Violent crime against children with disabilities: a nationwide prospective birth cohort-study. *Child Abuse Negl.* 2019;98:104150.
27. Breslau J, Miller E, Joanie Chung WJ, Schweitzer JB. Childhood and adolescent onset psychiatric disorders, substance use, and failure to graduate high school on time. *J Psychiatr Res.* 2011;45(3):295–301.
28. Fleming M, Fitton CA, Steiner MFC, McLay JS, Clark D, King A, et al. Educational and health outcomes of children treated for attention-deficit/hyperactivity disorder. *JAMA Pediatr.* 2017;171(7):e170691.
29. Korrel H, Mueller KL, Silk T, Anderson V, Sciberras E. Research review: language problems in children with attention-deficit hyperactivity disorder - a systematic meta-analytic review. *J Child Psychol Psychiatry.* 2017;58(6):640–54.
30. Lee SS, Humphreys KL, Flory K, Liu R, Glass K. Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/dependence: a meta-analytic review. *Clin Psychol Rev.* 2011;31(3):328–41.
31. Groenman AP, Janssen TWP, Oosterlaan J. Childhood psychiatric disorders as risk factor for subsequent substance abuse: a meta-analysis. *J Am Acad Child Adolesc Psychiatry.* 2017;56(7):556–69.
32. Sundquist J, Ohlsson H, Sundquist K, Kendler KS. Attention-deficit/hyperactivity disorder and risk for drug use disorder: a population-based follow-up and co-relative study. *Psychol Med.* 2015;45(5):977–83.
33. Jennum P, Hastrup LH, Ibsen R, Kjellberg J, Simonsen E. Welfare consequences for people diagnosed with attention deficit hyperactivity disorder (ADHD): a matched nationwide study in Denmark. *Eur Neuropsychopharmacol.* 2020;37:29–38.
34. Le HH, Hodgkins P, Postma MJ, Kahle J, Sikirica V, Setyawan J, et al. Economic impact of childhood/adolescent ADHD in a European setting: the Netherlands as a reference case. *Eur Child Adolesc Psychiatry.* 2014;23(7):587–98.
35. The social and economic costs of ADHD in Australia. Report prepared for the Australian ADHD Professionals Association. Canberra: Deloitte Access Economics; 2019.
36. Doshi JA, Hodgkins P, Kahle J, Sikirica V, Cangelosi MJ, Setyawan J, et al. Economic impact of childhood and adult attention-deficit/hyperactivity disorder in the United States. *J Am Acad Child Adolesc Psychiatry.* 2012;51(10):990–1002.e2.
37. de Graaf R, Kessler RC, Fayyad J, ten Have M, Alonso J, Angermeyer M, et al. The prevalence and effects of adult attention-deficit/hyperactivity disorder (ADHD) on the performance of workers: results from the WHO World Mental Health Survey Initiative. *Occup Environ Med.* 2008;65(12):835–42.
38. Swensen AR, Birnbaum HG, Secnik K, Marynchenko M, Greenberg P, Claxton A. Attention-deficit/hyperactivity disorder: increased costs for patients and their families. *J Am Acad Child Adolesc Psychiatry.* 2003;42(12):1415–23.
39. Libutzki B, Ludwig S, May M, Jacobsen RH, Reif A, Hartman CA. Direct medical costs of ADHD and its comorbid conditions on basis of a claims data analysis. *Eur Psychiatry.* 2019;58:38–44.
40. Hong M, Park B, Lee SM, Bahn GH, Kim MJ, Park S, et al. Economic burden and disability-adjusted life years (DALYs) of attention deficit/hyperactivity disorder. *J Atten Disord.* 2020;24(6):823–9.
41. Daley D, Jacobsen RH, Lange AM, Sorensen A, Walldorf J. The economic burden of adult attention deficit hyperactivity disorder: A sibling comparison cost analysis. *Eur Psychiatry.* 2019;61:41–8.
42. Du Rietz E, Jangmo A, Kuja-Halkola R, Chang Z, D'Onofrio BM, Ahnemark E, et al. Trajectories of healthcare utilization and costs of psychiatric and somatic multimorbidity in adults with childhood ADHD: a prospective register-based study. *J Child Psychol Psychiatry.* 2020;61(9):959–68.
43. Cortese S, Adamo N, Del Giovane C, Mohr-Jensen C, Hayes AJ, Carucci S, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *Lancet Psychiatry.* 2018;5(9):727–38.
44. Chang Z, Ghirardi L, Quinn PD, Asherson P, D'Onofrio BM, Larsson H. Risks and benefits of attention-deficit/hyperactivity disorder medication on behavioral and neuropsychiatric outcomes: a qualitative review of pharmacoepidemiology studies using linked prescription databases. *Biol Psychiatry.* 2019;86(5):335–43.
45. Coghill DR, Caballero B, Sorooshian S, Civil R. A systematic review of the safety of lisdexamfetamine dimesylate. *CNS Drugs.* 2014;28(6):497–511.
46. Cortese S, Holtmann M, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, et al. Practitioner review: current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. *J Child Psychol Psychiatry.* 2013;54(3):227–46.
47. Faraone SV, Po MD, Komolova M, Cortese S. Sleep-associated adverse events during methylphenidate treatment of attention-deficit/hyperactivity disorder: a meta-analysis. *J Clin Psychiatry.* 2019;80(3).
48. Graham J, Coghill D. Adverse effects of pharmacotherapies for attention-deficit hyperactivity disorder: epidemiology, prevention and management. *CNS Drugs.* 2008;22(3):213–37.
49. Storebø OJ, Ramstad E, Krogh HB, Nilausen TD, Skoog M, Holmskov M, et al. Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). *Cochrane Database Syst Rev.* 2015;(11):CD009885.
50. Storebø OJ, Pedersen N, Ramstad E, Kielsholm ML, Nielsen SS, Krogh HB, et al. Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents – assessment of adverse events in non-randomised studies. *Cochrane Database Syst Rev.* 2018;(5):CD012069.
51. Hollis C, Chen Q, Chang Z, Quinn PD, Viktorin A, Lichtenstein P, et al. Methylphenidate and the risk of psychosis in adolescents and young adults: a population-based cohort study. *Lancet Psychiatry.* 2019;6(8):651–8.
52. Man KK, Coghill D, Chan EW, Lau WC, Hollis C, Liddle E, et al. Methylphenidate and the risk of psychotic disorders and hallucinations in children and adolescents in a large health system. *Transl Psychiatry.* 2016;6(11):e956.
53. Solmi M, Fornaro M, Ostinelli EG, Zangani C, Croatto G, Monaco F, et al. Safety of 80 antidepressants, antipsychotics, anti-attention-deficit/hyperactivity medications and mood stabilizers in children and adolescents with psychiatric disorders: a large scale systematic meta-review of 78 adverse effects. *World Psychiatry.* 2020;19(2):214–32.
54. Faraone SV, Biederman J, Morley CP, Spencer TJ. Effect of stimulants on height and weight: a review of the literature. *J Am Acad Child Adolesc Psychiatry.* 2008;47(9):994–1009.
55. Carucci S, Balia C, Gagliano A, Lampis A, Buitelaar JK, Danckaerts M, et al. Long term methylphenidate exposure and growth in children and adolescents with ADHD: a systematic review and meta-analysis. *Neurosci Biobehav Rev.* 2020;120:509–25.
56. Dalsgaard S, Kvist AP, Leckman JF, Nielsen HS, Simonsen M. Cardiovascular safety of stimulants in children with attention-deficit/hyperactivity disorder: a nationwide prospective cohort study. *J Child Adolesc Psychopharmacol.* 2014;24(6):302–10.
57. Liang EF, Lim SZ, Tam WW, Ho CS, Zhang MW, McIntyre RS, et al. The effect of methylphenidate and atomoxetine on heart rate and systolic blood pressure in young people and adults with attention-deficit hyperactivity disorder (ADHD): Systematic review, meta-analysis, and meta-regression. *Int J Environ Res Public Health.* 2018;15(8):1789.
58. Liu H, Feng W, Zhang D. Association of ADHD medications with the risk of cardiovascular diseases: a meta-analysis. *Eur Child Adolesc Psychiatry.* 2019;28(10):1283–93.
59. Koren G, Barer Y, Ornoy A. Fetal safety of methylphenidate – a scoping review and meta analysis. *Reprod Toxicol.* 2020;93:230–4.
60. mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings: mental health Gap Action Programme (mhGAP) – version 2.0. Geneva: World Health Organization; 2016 (<https://apps.who.int/iris/handle/10665/250239>, accessed 6 June 2021).
61. Faraone SV, Rostain AL, Montano CB, Mason O, Antshel KM, Newcorn JH. Systematic review: nonmedical use of prescription stimulants: risk factors, outcomes, and risk reduction strategies. *J Am Acad Child Adolesc Psychiatry.* 2020;59(1):100–12.
62. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Fifth edition. Arlington, VA: American Ps

ychiatric Publishing; 2013.

63. Chinese Society of Psychiatry. Chinese classification and diagnostic criteria of mental disorder, 3rd edition. Jinan: Shandong Science and Technology Press; 2001.

64. Faraone SV, Asherson P, Banaschewski T, Biederman J, Buitelaar JK, Ramos-Quiroga JA, et al. Attention-deficit/hyperactivity disorder. Nat Rev Dis Primers. 2015;1:15020.

65. Feldman HM, Reiff MI. Clinical practice. Attention deficit-hyperactivity disorder in children and adolescents. N Engl J Med. 2014; 370(9):838–46.

66. Pearl PL, Weiss RE, Stein MA. Medical mimics. Medical and neurological conditions simulating ADHD. Ann N Y Acad Sci. 2001;931:97–112.

67. Stein MA. Medical mimics and differential diagnosis in adult ADHD. CNS Spectr. 2008;13(10 Suppl 15):14–6.

68. International statistical classification of diseases and related health problems, 11th revision. Geneva: World Health Organization; 2018 (<https://icd.who.int/en>, accessed 6 June 2021).

69. Yi Z, Jing L. Prevention and treatment guidelines for attention deficit hyperactivity disorder. Second edition. Beijing: Peking University Medical Press; 2015.

