REVIEW ARTICLE

Cardiovascular risk and pharmacotherapy in pediatric patients with attention-deficit hyperactivity disorder

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ABSTRACT

Mental health is one of the current pillars of global health; therefore, it is considered an essential factor in the well-being and quality of human life. The dramatic growth in the incidence and prevalence of mental disorders has brought about a burden of silent and unsustainable disease for healthcare systems, especially in younger age groups such as children and adolescents. Although major depressive disorder, anxious syndrome, and conduct and eating disorders are some of the most frequent in this age group, attention-deficit hyperactivity disorder (ADHD) is also an entity of interest affecting between 5 % and 10 % of children. There exists a pharmacological treatment for this condition, and it is based on stimulant and non-stimulant medications. Evidence of the highest quality has recently demonstrated that children and adolescents who were administered ADHD medications had a higher risk of some cardiovascular event compared to those who were not. Considering the impact and relevance of ADHD in the child and adolescent populations at present, as well as the use of drugs for its control, it is imperative to have evidence of the highest quality for decision-making in clinical practice. To date, there is no evidence in Spanish that has synthesized and analyzed this phenomenon. Based on the foregoing, the objective of this review is to analyze the most recent evidence of the association between cardiovascular risk and pharmacotherapy in pediatric patients with ADHD. A literature search was conducted using the search terms "Cardiovascular Risk," "Attention Deficit Hyperactivity Disorder," and "Pediatric," in addition to synonyms, which were combined with the operators "AND" and "OR," in the PubMed, ScienceDirect, Web of Science, and MEDLINE databases. After reviewing the most recent literature, it was identified that the quality of the current evidence regarding the association between increased cardiovascular risk secondary to pharmacotherapy in children and adolescents with ADHD is very low, heterogeneous, and fragmented. Nevertheless, the trend suggests that there may be a potential risk of the alteration of hemodynamic parameters, essentially heart rate and blood pressure, without involving the frequent or significant occurrence of serious cardiovascular adverse events. However, the evidence suggests continuous monitoring.

Keywords: Heart Disease Risk Factors; Drug Therapy; Attention Deficit Disorder with Hyperactivity; Child; Adolescent (Source: MeSH NLM).

INTRODUCTION

Mental health is one of the current pillars of global health and is considered an essential factor in the well-being and quality of human life [1]. The dramatic growth in the incidence and prevalence of mental disorders has brought about a burden of silent and unsustainable disease for healthcare systems, especially in younger age groups—such as children and adolescents—where neuropsychiatric manifestations and fatal outcomes are increasingly frequent [2]. An alarming transition of the burden of disease specifically among children and adolescents under 20 years of age has been described, reporting 21.5 million disability-adjusted life years (DALYs) by 2019 [3,4]. It is also estimated that this number will increase due to current environmental exposure and lifestyle [5]. Although major depressive, anxiety and eating disorders are some of the most common, attention-deficit hyperactivity disorder (ADHD) is also a condition of interest affecting 5 %-10 % of children and impacting the health outcomes of those affected [6].

ADHD is defined as a psychiatric disorder that compromises the functionality of affected individuals, due to a pattern

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characterized by inadequate levels of concentration, hyperactivity or impulsivity [7-9]. It is more common in children and adolescents, initially presenting with disorganization and inattentiveness at school age and during their development [10,11]. However, these manifestations lead to the category of a disorder only when they disrupt activities of daily living. To date, there are several treatments that have proven to be effective in controlling them, but they are not entirely safe [8,9]. Considering that the two available pharmacological groups are stimulants and non-stimulants, the side effects and adverse events range from hemodynamic and endocrine cycle alterations to the risk of dependence [7,12,13]. It has been previously described that these side effects and/or adverse events can have a significant influence on the quality of life of affected individuals. Although, there is another highly relevant adverse event: the cardiovascular risk associated with the use of ADHD medications [14-18].

Recent evidence of the highest quality demonstrated that children and adolescents who were administered ADHD medications had a higher risk of experiencing a cardiovascular event, compared to those who were not [18]. Considering the impact and relevance of ADHD in child and adolescent populations today, as well as the use of drugs to control it, it is crucial to have the best quality evidence for decision-making in healthcare practice, particularly in Spanish. Based on the foregoing, the objective of this review is to analyze the most recent evidence on the association between cardiovascular risk and pharmacotherapy in pediatric patients with ADHD.

SEARCH STRATEGY

A literature search was conducted using the search terms "Cardiovascular Risk," "Attention Deficit Hyperactivity Disorder" and "Pediatric," as well as synonyms, which were combined with the operators "AND" and "OR" in the PubMed, ScienceDirect, Web of Science and MEDLINE databases. We included all available full-text articles that evaluated the association between pharmacotherapy in pediatric patients with ADHD and cardiovascular risk, prioritizing original studies, systematic reviews and meta-analyses. Articles published up to the year 2023 were included. A total of 94 potentially relevant articles were identified, with a review of their titles and abstracts, of which 61 were finally included. The estimates and calculations found were presented in their original measures, whether as frequencies, percentages, confidence intervals (CI), mean difference (MD), relative risk (RR), odds ratio (*OR*) or hazard ratio (HR).

Effects of psychiatric medications on the cardiovascular system

To date, several mechanisms have been described that may be related to the instability of metabolic regulation and may have a direct influence on cardiovascular health [19-22]. Initially, it has been mentioned that many of these psychiatric drugs antagonize both H_1 and α_1-adrenergic and serotonergic receptors, which are related to appetite centers, thus resulting in increased food intake and weight gain [19]. This would explain why greater weight gain occurs with monoamine oxidase inhibitors and tricyclic antidepressants, which generate potent H_1 receptor antagonism. Additionally, these drugs interact with the regulation of leptin and adiponectin [20]. For example, lithium inhibits the enzyme glycogen synthase kinase-3 beta, and blocks the ability of leptin to reduce caloric intake, leading to weight gain. The use of sodium valproate has been found to have a dose-dependent inhibitory effect on the expression of adiponectin, which is a hormone that regulates glucose homeostasis and insulin sensitivity [21,22]. For this reason, its use could trigger an obesogenic and insulin-resistant process.

Other mechanisms are linked to dyslipidemia, as many of these drugs interact at the level of enzymes and lipid pathways related to the synthesis and degradation of these compounds [19]. Haloperidol, a typical antipsychotic, inhibits the cholesterol biosynthesis reaction catalyzed by reductases and isomerases. Clozapine and risperidone, atypical antipsychotics, also inhibit reductases and isomerases involved in this signaling pathway. Therefore, they have the potential to alter lipid metabolism by accumulating sterol intermediates and to cause dyslipidemia [23,24]. Another pharmacological group linked to this process is that of antidepressants, whose mechanism of action is related to the activation of sterol regulatory element binding protein (SREBP) transcription factors, involved in the biosynthesis of cholesterol and fatty acids [25,26].

An additional mechanism is insulin resistance, induced by several pharmacological groups such as second-generation antipsychotics, some of which increase serum glucose levels in a dose-dependent manner, as some of these molecules activate adenosine monophosphate (AMP)-dependent kinases in the hypothalamus, generating a gluconeogenic drive through the sympathetic nervous system [19,27]. This has been demonstrated by studies in biological models, in which an inhibitor of the aforementioned kinase was administered after these drugs, resulting in a reduction in hyperglycemia [28-30]. It is even presumed that there are unclear epigenetic mechanisms that may cause this hyperglycemic effect by impairing timely response to glucose homeostasis [19].

Finally, but not less importantly, psychotropic drugs with serotonergic $5HT_{2A}$ antagonist activity cause vascular contraction, increasing peripheral vascular resistance and, consequently, blood pressure [31]. Some drugs that interact with α_1-adrenergic receptors also cause an increase in blood

pressure levels through the same mechanism. Likewise, due to their anticholinergic effect, tricyclic antidepressants also contribute to increase blood pressure [32-34]. Psychostimulants, by releasing norepinephrine, dopamine and serotonin, have a positive effect on central dopaminergic and peripheral adrenergic centers, which influence this same hemodynamic parameter [33,34].

Thus, these factors, added to an unhealthy lifestyle, genetic load and environmental exposure, can undoubtedly trigger significant cardiometabolic damage which, in theory, could increase the cardiovascular risk of those who aggressively and continuously take certain psychiatric drugs (Figure 1). Therefore, risk analysis and assessment should be conducted on an individualized basis.

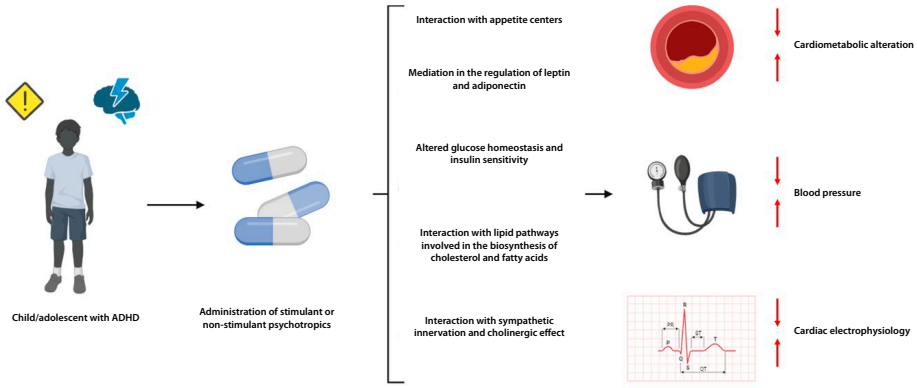

Figure 1. Mechanisms associated with hemodynamic, electrophysiological and cardiometabolic alterations in children and adolescents with ADHD and the administration of stimulant or non-stimulant psychotropics

Does the evidence support an increased cardiovascular risk secondary to ADHD medication among pediatric patients?

To date, the evidence concerning cardiovascular risk in children and adolescents receiving ADHD medication is scarce and exhibits varying degrees of fragmentation as to external validity. This is predominantly due to the fact that much of the evidence comes almost exclusively from high-income countries where outcome assessments differ.

One of the most recent studies was conducted by Huber et al. [35], who evaluated the change in serum lipoprotein levels in children and adolescents with ADHD receiving treatment, with a 10-year follow-up, in Germany. Methylphenidate was one of the most frequently identified drugs in this cohort. The researchers observed no baseline differences at the start of the analysis between the exposed group (n = 1,219) and the control group (n = 9,741) for cholesterol (p = 0.979), triglycerides (p = 0.412), low-density lipoproteins (LDL) (p = 0.525) and high-density lipoproteins (HDL) (p = 0.366). Interestingly, no changes were evident during the follow-up period, even in cases where methylphenidate was used. Therefore, the authors concluded that there was no association between ADHD medication, or the diagnosis itself, with alterations in lipid parameters suggesting any type of cardiovascular disorder [35]. Nevertheless, some years ago, Martinez-Raga et al. [36] suggested serious risks of vascular problems associated with this type of medication, specifically with stimulants such as methylphenidate and amphetamine derivatives, which had been shown to increase heart rate and blood pressure. In contrast, drugs such as clonidine or guanfacine, whether administered alone or in combination with other psychostimulants, have been shown to cause a decrease in these hemodynamic parameters without altering cardiac electrophysiology. However, by that time, it seemed that atomoxetine and α_2-adrenergic agonists presented a better benefit-risk balance as the risk of serious cardiovascular adverse events was extremely low [36].

Man et al. [37] published the most recent primary study (Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects - ADDUCE study; as of 2023), which explored the long-term outcomes of using methylphenidate in children and adolescents with ADHD and its association with chronic effects. This longitudinal controlled study was conducted in 27 specialized centers located across Germany, the United Kingdom, Italy, Switzerland and Hungary, including 1,410 individuals (756 in the methylphenidate group, 391 in the non-methylphenidate group and 263 in the control group) with average age of approximately nine years. During the 24 months of treatment and follow-up, the methylphenidate group did not show any difference compared to the non-methylphenidate group (p = 0.20) regarding the increased risk of adverse events. In spite of the fact that hemodynamic parameters such as heart rate and blood pressure were higher in the methylphenidate group, this was not associated with any relevant cardiovascular adverse events. Hence, the authors concluded that the use of this drug to treat ADHD in children and adolescents is safe, but continuous monitoring of hemodynamics should not be omitted [37].

Despite the uncertainty, existing systematic reviews and meta-analyses have only analyzed these events as secondary outcomes in nonspecific studies. A Cochrane Review published in 2018 [38], which included adverse events studied in non-randomized research conducted among children, adolescents and young adults (aged 3 to 20 years) with ADHD treated with methylphenidate, indicated, first, that the quality of the evidence found was very low, and, second, that methylphenidate increased by up to 36 % the risk of any serious adverse event (95 % CI: 1.17-1.57) related to psychotic disorder (95 % CI: 1.17-1.57), and up to 61 % the risk of arrhythmia (95 % CI: 1.48-1.74), compared to the control group. Additionally, the use of this drug was reported to increase sleep problems by 158 % (95 % CI: 1.24-5.34) and raise the risk of decreased appetite 15 times (95 % CI: 2.12-106.83) [38]. Up to this point in time, it was suggested—based on limited rationale—that methylphenidate might be associated with a significant number of serious and nonserious adverse events. As of 2023, this same review was updated [39], this time including more than 30,000 individuals with a mean age of 10 years and average treatment duration with methylphenidate of 29 days. Unlike the previous review, this one found that methylphenidate did not modify the risk of serious adverse events (RR 0.80; 95 % CI: 0.39-1.67), although this estimate obtained a very low certainty. Similarly, regarding whether it could cause nonserious adverse events compared to placebo or no intervention (RR 1.23; 95 % CI 1.11-1.37), the certainty was also very low [34]. Thus, these reviews have been inconclusive and imprecise due to the low quality of the evidence.

Slightly different from the previous approach, Cerrillo-Urbina et al. [39] conducted a meta-analysis of randomized controlled trials that assessed the safety and efficacy of stimulant and non-stimulant drugs among children and adolescents with ADHD, including 15 trials with a total of 4,648 individuals aged 6 to 17 years. Although both pharmacological groups were found to be effective for symptom control, the most frequent adverse events in the stimulant and non-stimulant groups were decreased appetite (28.6 % vs. 14.2 %) and altered sleep quality (4.4 % vs. 34.1 %), respectively [39].

The remaining available evidence from qualitative reviews differs in approach, showing inconclusive results and numerous hypotheses without solid support, whether from basic, clinical or translational research [40-44]. Zhang et al. [18] may be the authors with the most robust and transparent evidence to date concerning the cardiovascular risk from ADHD medication. Despite this analysis comprised children, adolescents, and adults (more than 3 million individuals drawn from 19 studies), it had a median follow-up of 1.5 years. The overall analysis demonstrated that there was no association between the use of any medication with cardiovascular disease in children or adolescents (RR 1.18; 95 % CI 0.91-1.5), or adults (RR 1.04; 95 % CI 0.43-2.48). When analyzed by pharmacological group, no association was found for stimulants (RR 1.24; 95 % CI 0.84-1.83) or non-stimulants (RR 1.22; 95 % CI 0.25-5.97). Likewise, when analyzing by cardiovascular condition, such as, e.g., arrhythmia or cardiac arrest (RR 1.60; 95 % CI 0.94-2.72), cerebrovascular disease (RR 0.91; 95 % CI 0.72-1.1) or acute myocardial infarction (RR 1.06; 95 % CI 0.68-1.65), no associations were found. This allowed the researchers to conclude that there is no association between the use of ADHD drugs and increased cardiovascular risk [18]. However, it should be noted that the follow-up period was quite short. Therefore, the evidence to answer this research question remains weak and very heterogeneous.

Future perspectives

In view of the dramatic transition with a growing trend in the prevalence and incidence of mental disorders—such as ADHD—particularly in children and adolescents, various authors have proposed relevant and consistent lines of study in accordance with global health needs [45-49]. The safety and efficacy of novel molecules, as well as the pluralism and identification of ADHD phenotypes, particularly in preschool children, are essential for the early approach, preventing the condition from progressing to severe manifestations and affecting the neurodevelopment of children or adolescents [50]. Priority should be given to translational research aimed at gaining a deeper understanding of new phenotypes or clustered phenotypes, as well as the search for biomarkers and new signaling pathways to identify increasingly precise therapeutic targets [51-54]. This type of research should be encouraged with funding support from the government, private enterprises and higher education institutions, which should also provide comprehensive training for healthcare professionals. This training should emphasize mental disorders, enabling them to rigorously and precisely address the burden of disease that is faced in silence.

At present, multidomain computerized models based on neuroimaging studies are being developed to help understand the affected brain areas [55-57] in order to facilitate the approach to pharmacological, occupational, psychiatric and psychological therapies. This is the perfect time to study these conditions in developing countries, where there is a significant evidence gap, as well as a lack of highly specialized centers for widespread treatment of patients with ADHD. In addition, such centers would serve as sites for conducting randomized controlled trials to evaluate the safety, efficacy and efficiency of ADHD drugs [59-64] and their association with long-term cardiovascular, neurological and psychiatric outcomes, taking into account the health context of each region [65]. Timely and specialized access to mental healthcare is a dilemma faced by health systems [66,67], for which upcoming development plans and health strategies should align with the

needs expressed by international organizations and scientific societies, in order to act at the local and national levels but with the potential to contribute to the scientific evidence at the international level [68,69].

CONCLUSIONS

Although the quality of the current evidence regarding the association between increased cardiovascular risk secondary to pharmacotherapy in children and adolescents with ADHD is very low, heterogeneous and fragmented, the trend suggests that there may be a potential risk in the alteration of hemodynamic parameters, essentially heart rate and blood pressure, without involving the frequent or significant occurrence of serious adverse cardiovascular events. However, the evidence suggests the need for continuous monitoring.

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BIBLIOGRAPHIC REFERENCES

1. Piao J, Huang Y, Han C, Li Y, Xu Y, Liu Y, et al. Alarming changes in the global burden of mental disorders in children and adolescents from 1990 to 2019: a systematic analysis for the Global Burden of Disease study. Eur Child Adolesc Psychiatry [Internet]. 2022;31(11):1827-45.
2. Baranne ML, Falissard B. Global burden of mental disorders among children aged 5-14 years. Child Adolesc Psychiatry Ment Health [Internet]. 2018;12:19.
3. Chen YL, Kuo RN, Gau SS. Burden of mental disorders in children in the general population and in health facilities: discrepancies in years lived with disability based on national prevalence estimates between populations receiving care or not. Eur Child Adolesc Psychiatry [Internet]. 2022;31(8):1-9.
4. Hossain MM, Nesa F, Das J, Aggad R, Tasnim S, Bairwa M, et al. Global burden of mental health problems among children and adolescents during COVID-19 pandemic: an umbrella review. Psychiatry Res [Internet]. 2022;317:114814.
5. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry [Internet]. 2022;9(2):137-50.
6. Vasileva M, Graf RK, Reinelt T, Petermann U, Petermann F. Research review: a meta-analysis of the international prevalence and comorbidity of mental disorders in children between 1 and 7 years. J Child Psychol Psychiatry [Internet]. 2021;62(4):372-81.
7. Magnus W, Nazir S, Anilkumar AC, Shaban K. Attention deficit hyperactivity disorder [Internet]. Florida: StatPearls; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441838/
8. Carbray JA. Attention-deficit/hyperactivity disorder in children and adolescents. J Psychosoc Nurs Ment Health Serv [Internet]. 2018;56(12):7-10.
9. Drechsler R, Brem S, Brandeis D, Grünblatt E, Berger G, Walitza S. ADHD: Current concepts and treatments in children and adolescents. Neuropediatrics [Internet]. 2020;51(5):315-5.
10. Kazda L, Bell K, Thomas R, McGeechan K, Sims R, Barratt A. Overdiagnosis of attention-deficit/hyperactivity disorder in children and adolescents: a systematic scoping review. JAMA Netw Open [Internet]. 2021;4(4):e215335.
11. Otasowie J, Castells X, Ehimare UP, Smith CH. Tricyclic antidepressants for attention deficit hyperactivity disorder (ADHD) in children and adolescents. Cochrane Database Syst Rev [Internet]. 2014;(9).
12. Vierhile AE, Palumbo D, Belden H. Diagnosis and treatment of attention deficit hyperactivity disorder. Nurse Pract [Internet]. 2017;42(10):48-54.
13. Mueller A, Sawicki OA, Günther MP, Glushan A, Witte C, Klaaßen-Mielke R, et al. General practitioner-centred paediatric primary care reduces risk of hospitalisation for mental disorders in children and adolescents with ADHD: findings from a retrospective cohort study. Eur J Gen Pract [Internet]. 2022;28(1):150-6.
14. Marano G, Traversi G, Romagnoli E, Catalano V, Lotrionte M, Abbate A, et al. Cardiologic side effects of psychotropic drugs. J Geriatr Cardiol [Internet]. 2011;8(4):243-53.
15. Potočnjak I, Degoricija V, Vukičević Baudoin D, Čulig J, Jakovljević M. Cardiovascular side effects of psychopharmacologic therapy. Int J Cardiol [Internet]. 2016;219:367-72.
16. Mackin P. Cardiac side effects of psychiatric drugs. Hum Psychopharmaco [Internet]. 2008;23(1):3-14.
17. Scheifes A, Walraven S, Stolker JJ, Nijman HL, Egberts TC, Heerdink ER. Adverse events and the relation with quality of life in adults with intellectual disability and challenging behaviour using psychotropic drugs. Res Dev Disabil [Internet]. 2016;49-50:13-21.
18. Zhang L, Yao H, Li L, Du Rietz E, Andell P, Garcia-Argibay M, et al. Risk of cardiovascular diseases associated with medications used in attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. JAMA Netw Open [Internet]. 2022;5(11):e2243597.
19. Abosi O, Lopes S, Schmitz S, Fiedorowicz JG. Cardiometabolic effects of psychotropic medications. Horm Mol Biol Clin Investig [Internet]. 2018;36(1).
20. Graham J, Coghill D. Adverse effects of pharmacotherapies for attention-deficit hyperactivity disorder: epidemiology, prevention and management. CNS Drugs [Internet]. 2008;22(3):213-37.
21. 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 [Internet]. 2019;86(5):335-43.
22. Pan PY, Jonsson U, Şahpazoğlu Çakmak SS, Häge A, Hohmann S, Nobel Norrman H, et al. Headache in ADHD as comorbidity and a side effect of medications: a systematic review and meta-analysis. Psychol Med [Internet]. 2022;52(1):14-25.
23. Reddy DS. Current pharmacotherapy of attention deficit hyperactivity disorder. Drugs Today [Internet]. 2013;49(10):647-65.
24. 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

[Internet]. 2013;54(3):227-46.
25. Gémes K, Taipale H, Björkenstam E, Rahman S, Gustafsson K, Tanskanen A, et al. The role of sociodemographic and clinical factors in the initiation and discontinuation of attention deficit hyperactivity disorder medication among young adults in Sweden. Front Psychiatry [Internet]. 2023;14:1152286.
26. Ogundele MO, Ayyash HF. ADHD in children and adolescents: Review of current practice of non-pharmacological and behavioural management. AIMS Public Health [Internet]. 2023;10(1):35-51.
27. 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 [Internet]. 2018;5(9):727-38.
28. Ikegami M, Ikeda H, Ohashi T, Ohsawa M, Ishikawa Y, Kai M, et al. Olanzapine increases hepatic glucose production through the activation of hypothalamic adenosine 5'-monophosphate-activated protein kinase. Diabetes Obes Metab [Internet]. 2013;15(12):1128-35.
29. Osland ST, Steeves TD, Pringsheim T. Pharmacological treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders. Cochrane Database Syst Rev [Internet]. 2018;6(6):CD007990.
30. Hennissen L, Bakker MJ, Banaschewski T, Carucci S, Coghill D, Danckaerts M, et al. Cardiovascular effects of stimulant and non-stimulant medication for children and adolescents with ADHD: a systematic review and meta-analysis of trials of methylphenidate, amphetamines and atomoxetine. CNS Drugs [Internet]. 2017;31(3):199-215.
31. Liu Q, Zhang H, Fang Q, Qin L. Comparative efficacy and safety of methylphenidate and atomoxetine for attention-deficit hyperactivity disorder in children and adolescents: meta-analysis based on head-to-head trials. J Clin Exp Neuropsychol [Internet]. 2017;39(9):854-65.
32. 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 [Internet]. 2018;15(8):1789.
33. King S, Griffin S, Hodges Z, Weatherly H, Asseburg C, Richardson G, et al. A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents. Health Technol Assess [Internet]. 2006;10(23).
34. 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 [Internet]. 2023;3(3):CD009885.
35. Huber F, Schulz J, Schlack R, Hölling H, Ravens-Sieberer U, Meyer T, et al. Long-term changes in serum levels of lipoproteins in children and adolescents with attention-deficit/hyperactivity disorder (ADHD). J Neural Transm [Internet]. 2023;130(4):597-609.
36. Martinez-Raga J, Knecht C, Szerman N, Martinez MI. Risk of serious cardiovascular problems with medications for attention-deficit hyperactivity disorder. CNS Drugs [Internet]. 2013;27(1):15-30.
37. Man KKC, Häge A, Banaschewski T, Inglis SK, Buitelaar J, Carucci S, et al. Long-term safety of methylphenidate in children and adolescents with ADHD: 2-year outcomes of the Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects (ADDUCE) study. Lancet Psychiatry [Internet]. 2023;10(5):323-33
38. 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 [Internet]. 2018;5(5):CD012069.
39. Cerrillo-Urbina AJ, García-Hermoso A, Pardo-Guijarro MJ, Sánchez-López M, Santos-Gómez JL, Martínez-Vizcaíno V. The effects of long-acting stimulant and nonstimulant medications in children and adolescents with attention-deficit/hyperactivity disorder: a meta-analysis of randomized controlled trials. J Child Adolesc Psychopharmacol [Internet]. 2018;28(8):494-507.
40. Topriceanu CC, Moon JC, Captur G, Perera B. The use of attention-deficit hyperactivity disorder medications in cardiac disease. Front Neurosci [Internet]. 2022;16:1020961.
41. Berger S. Attention deficit hyperactivity disorder medications in children with heart disease. Curr Opin Pediatr [Internet]. 2016;28(5):607-12.
42. Neuchat EE, Bocklud BE, Kingsley K, Barham WT, Luther PM, Ahmadzadeh S, et al. The role of alpha-2 agonists for attention deficit hyperactivity disorder in children: a review. Neurol Int [Internet]. 2023;15(2):697-707.
43. Torres-Acosta N, O'Keefe JH, O'Keefe CL, Lavie CJ. Cardiovascular effects of ADHD therapies: JACC review topic of the week. J Am Coll Cardiol [Internet]. 2020;76(7):858-66.
44. Bange F, Le Heuzey MF, Acquaviva E, Delorme R, Mouren MC. Cardiovascular risks and management during attention deficit hyperactivity disorder treatment with methylphenidate. Arch Pediatr [Internet]. 2014;21(1):108-12.
45. Gaynes B, Christian R, Saavedra L, Wines R, Jonas D, Vishwanathan M,et al. Future research needs for attention deficit hyperactivity disorder: effectiveness of treatment in at-risk preschoolers; long-term effectiveness in all ages; and variability in prevalence, diagnosis, and treatment: Version 2. 9 a ed. Estados Unidos: Rockville MD; 2012.
46. Park TW, Baul TD, Morgan JR, Wilens TE, Yule AM. Trends in attention-deficit hyperactivity disorder diagnosis and pharmacotherapy among adults with opioid use disorder. Psychiatr Serv [Internet]. 2024; 75(3):214-20.
47. Pouchon A, Nasserdine R, Dondé C, Bertrand A, Polosan M, Bioulac S. A systematic review of pharmacotherapy for attention-deficit/hyperactivity disorder in children and adolescents with bipolar disorders. Expert Opin Pharmacother [Internet]. 2023;24(13):1497-509.
48. Lin CC, Chung CH, Chien WC, Tzeng NS. Pharmacotherapy may attenuate the risk of child abuse in attention-deficit/hyperactivity disorder from the real-world evidence. J Child Adolesc Psychopharmacol [Internet]. 2023;33(2):59-68.
49. Coetzee C, Schellekens AFA, Truter I, Meyer A. Effect of past pharmacotherapy for attention-deficit/hyperactivity disorder on substance use disorder. Eur Addict Res [Internet]. 2023;29(1):9-18.
50. Dutta CN, Christov-Moore L, Ombao H, Douglas PK. Neuroprotection in late life attention-deficit/hyperactivity disorder: a review of pharmacotherapy and phenotype across the lifespan. Front Hum Neurosci [Internet]. 2022;16:938501.
51. Newcorn JH, Wilens TE. So what really is new in the pharmacotherapy of attention-deficit/hyperactivity disorder? Child Adolesc Psychiatr Clin N Am [Internet]. 2022;31(3):13-4.
52. Joshi G, Wilens TE. Pharmacotherapy of attention-deficit/hyperactivity disorder in individuals with autism spectrum disorder. Child Adolesc Psychiatr Clin N Am [Internet]. 2022;31(3):449-68.
53. Akmatov MK, Holstiege J, Bätzing J. Secular trends and regional variations in pharmacotherapy of attention-deficit/hyperactivity disorder (ADHD) among children and adolescents in Germany. BMC Psychiatry [Internet]. 2021;21(1):405.

54. Gregório J, Ferreira R, Fernandes AS. The perception of primary school teachers regarding the pharmacotherapy of attention-deficit hyperactivity disorder. Int J Environ Res Public Health [Internet]. 2021;18(12):6233.
55. Chamberlain SR, Robbins TW, Winder-Rhodes S, Müller U, Sahakian BJ, Blackwell AD, et al. Translational approaches to frontostriatal dysfunction in attention-deficit/hyperactivity disorder using a computerized neuropsychological battery. Biol Psychiatry [Internet]. 2011;69(12):1192-203.
56. De la Peña IC, Pan MC, Thai CG, Alisso T. Attention-deficit/hyperactivity disorder predominantly inattentive subtype/presentation: Research Progress and Translational Studies. Brain Sci [Internet]. 2020;10(5):292.
57. Leitner Y, Doniger GM, Barak R, Simon ES, Hausdorff JM. A novel multidomain computerized cognitive assessment for attention-deficit hyperactivity disorder: evidence for widespread and circumscribed cognitive deficits. J Child Neurol [Internet]. 2007;22(3):264-76.
58. Advokat C. What are the cognitive effects of stimulant medications? Emphasis on adults with attention-deficit/hyperactivity disorder (ADHD). Neurosci Biobehav Rev [Internet]. 2010;34(8):1256-66.
59. Sharif S, Guirguis A, Fergus S, Schifano F. The use and impact of cognitive enhancers among university students: a systematic review. Brain Sci [Internet]. 2021;11(3):355.
60. Becke M, Tucha L, Weisbrod M, Aschenbrenner S, Tucha O, Fuermaier ABM. Non-credible symptom report in the clinical evaluation of adult ADHD: development and initial validation of a new validity index embedded in the Conners' adult ADHD rating scales. J Neural Transm [Internet]. 2021;128(7):1045-63.
61. Mandali A, Sethi A, Cercignani M, Harrison NA, Voon V. Shifting uncertainty intolerance: methylphenidate and attention-deficit hyperactivity disorder. Transl Psychiatry [Internet]. 2021;11(1):12.
62. World Health Organization. Mental Health [Internet]. Ginebra: WHO;2023. Available from: https://www.who.int/health-topics/mental-health#tab=tab_1
63. Collins PY. What is global mental health? World Psychiatry [Internet]. 2020;19(3):265-66.
64. Patel V, Prince M. Global mental health: a new global health field comes of age. JAMA [Internet]. 2010;303(19):1976-7.
65. The Global Goals. Good health and well-being [Internet]. California: The Global Goals; 2023. Available from: https://www.globalgoals.org/goals/3-good-health-and-well-being/
66. Dakić T. Mental health burden and unmet needs for treatment: a call for justice. Br J Psychiatry [Internet]. 2020;216(5):241-2.
67. Schuklenk U. Access to mental health care - a profound ethical problem in the global south. Dev World Bioeth [Internet]. 2020;20(4):174.
68. Raviola G, Becker AE, Farmer P. A global scope for global health-including mental health. Lancet [Internet]. 2011;378(9803):1613-5.
69. The Lancet. Movement for global mental health gains momentum. Lancet [Internet]. 2009;374(9690):587.

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