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Analysis of adverse reactions related to the use of methylphenidate: An integrative review of the literature

Análise das reações adversas relacionadas ao uso do metilfenidato: Revisão integrativa da literatura

Análisis de reacciones adversas relacionadas con el uso de metilfenidato: Una revisión integradora de la literatura

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Abstract
Methylphenidate is a stimulant of the Central Nervous System (CNS) used worldwide in the treatment of Attention Deficit/Hyperactivity Disorder (ADHD), which acts mainly by blocking the dopamine transporter (DAT), inhibiting the reuptake of dopamine by SRIs, causing improvement in ADHD symptoms. When carrying out treatment with Methylphenidate, potential adverse effects may arise. This study aimed to analyze the main adverse reactions cited in other literature on Methylphenidate, to evaluate its safety. This is an Integrative Literature Review Study, carried out from the selection of articles that covered the proposed objectives, with results that show the authors' assessments of adverse reactions related to the use of Methylphenidate. Among the effects observed, psychotic effects, speech changes, tics, cardiovascular risks, and growth retardation are associated with the use of Methylphenidate. From this, it is concluded that effects such as vascular risks, growth retardation, mania, changes in speech, and others related to psychotic effects may be present in patients undergoing treatment with Methylphenidate, impacting the quality of life of those who use it.
Keywords: Methylphenidate; Pharmacovigilance; Adverse reactions.

Resumo
O metilfenidato é um estimulante do Sistema Nervoso Central (SNC) utilizado mundialmente no tratamento do Transtorno de Déficit de Atenção/Hiperatividade (TDAH), que atua principalmente bloqueando o transportador de dopamina (DAT), inibindo a recaptação de dopamina pelas SRCs, levando à melhora dos sintomas de TDAH. Ao se submeter ao tratamento com metilfenidato, podem surgir potenciais efeitos adversos. O estudo tem como objetivo analisar as principais reações adversas citadas em outra literatura sobre o Metilfenidato, com vistas a avaliar sua segurança. Trata-se de um Estudo de Revisão Integrativa da Literatura, realizado a partir da seleção de artigos que contemplaram os objetivos propostos, com resultados que mostram as avaliações dos autores sobre as reações

adversas relacionadas ao uso do Metilfenidato. Dentre os efeitos observados, efeitos psicóticos, distúrbios da fala, tiques, riscos cardiovasculares e retardo de crescimento estão relacionados ao uso do metilfenidato. A partir disso, conclui-se que efeitos como: riscos vasculares, retardo de crescimento, mania, alterações de fala e outros relacionados a efeitos psicóticos podem estar presentes em pacientes que são tratados com Metilfenidato, impactando na qualidade de vida daqueles que o utilizam.
Palavras-chave: Metilfenidato; Farmacovigilância; Reações adversas.

Resumen
El metilfenidato es un estimulante del Sistema Nervioso Central (SNC) utilizado a nivel mundial en el tratamiento del Trastorno por Déficit de Atención e Hiperactividad (TDAH), que actúa principalmente bloqueando el transportador de dopamina (DAT), inhibiendo la recaptación de dopamina por parte de los SRI, provocando una mejora en los síntomas del TDAH. Pueden surgir posibles efectos adversos durante el tratamiento con metilfenidato. El objetivo principal del estudio es analizar las principales reacciones adversas citadas en otra literatura sobre el metilfenidato, con el fin de evaluar su seguridad. Se trata de un Estudio Integrador de Revisión de la Literatura, realizado a partir de la selección de artículos que cubrieron los objetivos propuestos, con resultados que muestran las evaluaciones de los autores sobre las reacciones adversas relacionadas con el uso de Metilfenidato. Entre los efectos observados, los efectos psicóticos, los trastornos del habla, los tics, los riesgos cardiovasculares y el retraso del crecimiento están relacionados con el uso de metilfenidato. De lo anterior, se concluye que efectos como: riesgos vasculares, retraso del crecimiento, manía, cambios en el habla y otros relacionados con efectos psicóticos pueden estar presentes en pacientes tratados con Metilfenidato, impactando en la calidad de vida de quienes lo utilizan.
Palabras clave: Metilfenidato; Farmacovigilancia; Reacciones adversas.

1. Introduction

Methylphenidate is a central nervous system stimulant used in the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) classified as a neurodevelopmental disorder, which begins in childhood and is determined by harmful levels of inattention, disorganization, hyperactivity, and impulsivity (American Psychiatric Association, 2014). In addition, it is indicated for the treatment of narcolepsy, a chronic sleep disorder that causes excessive sleepiness during the day. This stimulant is known for its commercial products: Ritalin, Concerta and Bifentin, useful for improving several symptoms related to ADHD, namely: distraction, short attention span, hyperactivity, emotional lability, and impulsivity (*Canadian ADHD Practice Guidelines*, 2014). Used worldwide in order to treat ADHD, Methylphenidate blocks the dopamine transporter (DAT), inhibiting the reuptake of dopamine by SRIs (Touafchia et al., 2020). The relationship between this mechanism and its action can be observed in paradoxical drug-related effects, as the optimal levels of dopamine to perform cognitive functions vary from person to person (Ekhart et al., 2021).

In this regard, it is important to note that Methylphenidate acts as an inhibitor of norepinephrine and dopamine reuptake, increasing the presence of these neurotransmitters in the extraneuronal space and prolonging their action, leading to improvement in the main and behavioral symptoms associated with ADHD (Goodman & Gilman, 2012). According to Storebo et al. (2023) it improves ADHD symptoms, favoring a beneficial effect on overall behavior, and decreasing symptoms such as hyperactivity and inattention.

Thus, cardiovascular assessment, mental and physical health, as well as social circumstances should be considered before starting medication, so that treatment is as appropriate as possible (ŞIMŞEK et al., 2022). However, the use indiscriminately by healthy people who seek cognitive improvement is also part of the current scenario. Therefore, they disregard the harmful effects that may arise, since this drug has no proven efficacy in individuals without a diagnosis, who do not need to use it (Sumerakanwal et al., 2021).

Thus, when undergoing treatment with Methylphenidate, potential side effects may arise, including insomnia, reduced appetite, headache and abdominal pain (Adesman & Morgan, 1999). In addition to these above-mentioned reactions, other adverse effects may appear after treatment, ocular reactions such as glaucoma, and increased myopic values of static

retinoscopy and axial length. Likewise, other effects such as decreased appetite, difficulty sleeping, headache, mood swings, and anxiety can also arise, these being more common (Nanda et al., 2023).

For adverse effects to be monitored, pharmacovigilance systems provide methods for these reactions to be evidenced and, consequently, important information about the drug to be known. An example of this is vigilance is the National System of Notifications in Health Surveillance (NOTIVISA), a system of spontaneous notifications of suspected adverse drug reactions in Brazil (Mota, Vigo, & Kuchenbecker, 2019). Additionally, VigiAcess is an example of such systems, as it provides relevant data for those who want to understand the side effects that may arise after using medications. Thus, taking into account the data presented by VigiAcess, the most frequent adverse reactions in the use of methylphenidate are: General disorders and conditions at the site of administration (23%), followed by Injuries, poisoning and procedural complications (14%) and Psychiatric disorders (14%) (*VigiAccess*, n.d.).

In view of the above, it is important to understand the safety of Methylphenidate from the analysis of adverse effects, since this drug is widely used in the treatment of ADHD and many adverse effects can be part of the daily life of those who use it irrationally or not. Therefore, the present study is justified by the need to understand the potential adverse effects and prevent the misuse of this drug.

This article aimed to analyze the main adverse reactions cited in other literature on Methylphenidate, to evaluate its safety. Therefore, more specifically, it seeks to identify the profile of users of this drug and understand its mechanism of action, analyze the frequency of adverse reactions to this drug from pharmacovigilance platforms and articles, evaluate the impact of this drug on the lives of users and the most reported adverse reactions, and compare the results obtained among the articles found.

2. Methodology

This is an Integrative Literature Review Study (Crossetti, 2012) aimed at identifying scientific productions on the adverse effects caused by Methylphenidate, carried out between April and May 2024. The choice of the integrative review method is based on its ability to facilitate the search and critical evaluation of various methodological approaches, in addition to the synthesis of the available evidence on the topic in question. The objective is to develop a comprehensive explanation of a specific phenomenon, implement interventions, and identify gaps that can guide future investigations (Souza et al., 2010).

According to Souza et al. (2010), the elaboration of an integrative review involves, in general, the execution of six distinct stages, which are analogous to the phases of development of conventional research. Thus, the following steps were used in the Integrative Literature Review: 1st Formulation of the guiding question; 2nd Literature review and definition of inclusion and exclusion criteria; 3rd Data collection; 4th Critical evaluation of the selected studies; 5th Interpretation of the results; and 6th Presentation of the review. For the study, the Virtual Health Library (VHL) and PubMED were used to search for articles. Thus, articles were selected from the following electronic databases: Medline and PubMed. For the research, the Health Sciences Descriptors (DeSC.) in English were used: "Methylphenidate", "Pharmacovigilance" combined by the Boolean operator "AND".

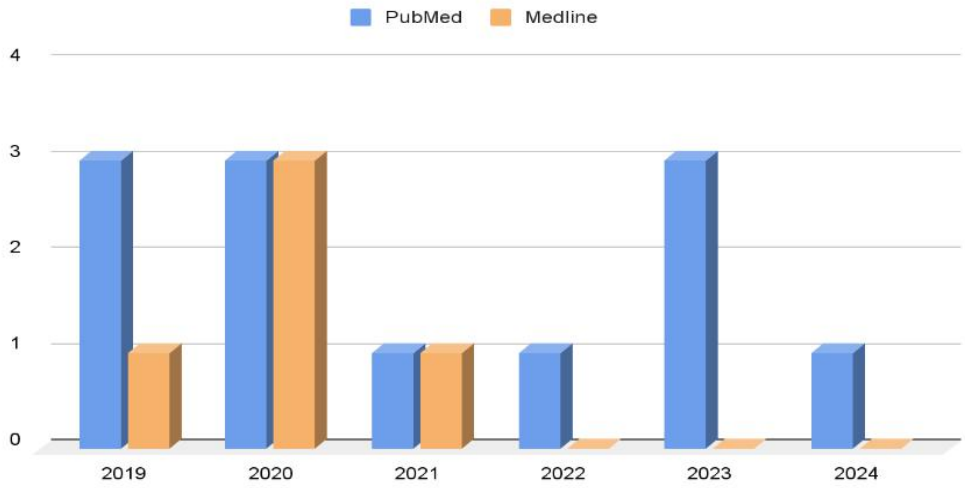
For the inclusion criteria, the search was limited to articles published in the last five years, from April 2019 to May 2024. To ensure the relevance and timeliness of the data, "*open access*" articles were selected, in English, Portuguese and French. Thus, the types of study were risk factors, etiology study, observational study, prognostic study, incidence study, controlled clinical trial, diagnostic study, and qualitative research. Some selected articles were not open access in the databases, but were made available through CAFe access, in the collection of CAPES Journal Portal. With the exclusion

criteria, literature reviews, incomplete studies, language studies that were not determined, repeated articles and that did not meet the objectives proposed by the study were excluded, based on the reading of the abstract.

3. Results and Discussion

From this search, 17 articles that met the exclusion and inclusion criteria were pre-selected. Among them, there were 5 articles from the Medline database and 12 articles from PubMed. Therefore, the numbers of articles mentioned can be viewed according to their year of publication, in Graph 1, below:

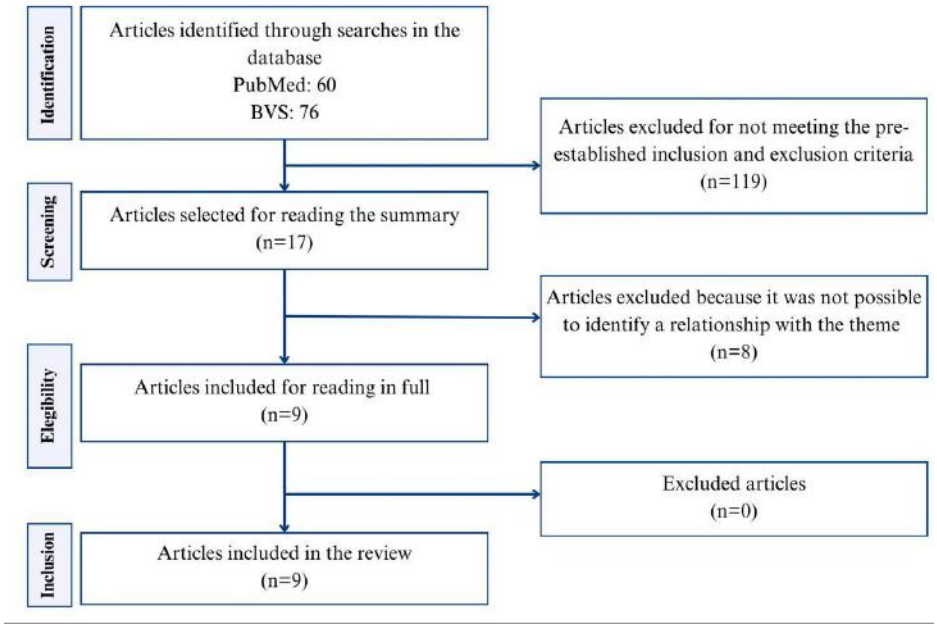
Graph 1 — Publications in chronological order, according to the descriptors used.



Source: Authorship (2024).

The graph presented above (Graph 1) shows, in detail, the year corresponding to the articles found in each database. After identifying the articles, a previous analysis was carried out by reading the title and abstract, resulting in the selection of 9 articles that contemplated the objectives of the present study, as presented in Flowchart 1.

Flowchart 1 - Process of selection of articles and application of database filters for this literature review.



Source: Authorship (2024).

The flowchart shown above demonstrates in detail the process of selecting the articles, from the identification of the records in the databases to the inclusion of the studies. The articles were characterized in order to establish the main information and their respective results. Thus, this characterization was carried out according to the variables: Author, Year, DOI, Title, Objective and Results, which can be seen in Chart 1, below:

Chart 1 - Characterization of the studies selected for this literature review.

Author, Year.	DOI	Title	Objective	Results
Wei et al., 2023.	10.3389/fphar.2023.1208456	Safety profiles of methylphenidate, amphetamine, and atomoxetine: analysis of spontaneous reports submitted to the food and drug administration adverse event reporting system	Examine differences in adverse events between methylphenidate, atomoxetine, and Amphetamine.	Methylphenidate has been associated with myocardial infarction, acute myocardial infarction, coronary artery dissection, QT prolongation on the electrocardiogram, growth retardation, self-destructive behavior, suicidal ideation, and completed suicide.
Montastruc, 2022.	10.1111/bcp.15470	Fatal adverse drug reactions in children: A descriptive study in the World Health Organization pharmacovigilance database, 2010–2019	The aim of the present study to investigate the main drugs involved in fatal outcomes using the World Health Organization (WHO) pharmacovigilance database, VigiBase.	Fatal ADRs with methylphenidate have been associated primarily with cardiac and/or respiratory arrest and about 50% of sudden death in children.
Dubrall et al., 2021.	10.1186/s4036 0-021-00520-y	Descriptive analysis of adverse drug reaction reports in children and adolescents from Germany: frequently reported reactions and suspected drugs	The aim of study was to analyze the drugs and ADRs reported most frequently in ADR reports from Germany referring to children contained in the European ADR database (EudraVigilance).	Adverse reactions of methylphenidate were most frequently reported in males aged 4 to 17 years. Symptoms: headache, decreased appetite and tachycardia were the most reported with methylphenidate.

Soyer et al., 2019.	10.1093/pch/pxz012	Visual disorders with psychostimulants: A paediatric case report	The aim of this study was to analyze a case of visual disorders with psychostimulants.	Long-term use of methylphenidate may cause changes in the lens in a dose-related manner.
Trenque et al., 2019	10.1111/bcp.14097	Methylphenidate and stuttering	Investigate whether there is evidence of an increased risk of stuttering with MPH treatment in a large pharmacovigilance database, using disproportionality analysis.	This study found evidence in favor of a significant relationship between HPM treatment and the occurrence of speech disorders, specifically stuttering.
Hollis et al., 2019.	10.1016/S2215−0366(19)30189-0	Methylphenidate and the risk of psychosis in adolescents and young adults: a population-based cohort study	To examine the risk of psychotic events immediately after initiating methylphenidate treatment in adolescents and young adults with and without a previously diagnosed psychotic disorder. And second, examine the long-term outcomes of methylphenidate exposure 1 year after starting treatment on the risk of psychosis.	No evidence was found that initiation of methylphenidate treatment increases the risk of psychotic events in adolescents and young adults, including those with a history of psychosis.
Hamard J et al., 2024	10.1136/bmjment-2023-300876	Psychosis with use of amphetamine drugs, methylphenidate and atomoxetine in adolescent and adults.	The objective of this study was to collect information from the WHO's Global Individual Case Safety Reports database, to assess whether the use of amphetamines or atomoxetine is associated with a higher risk of reporting symptoms of psychosis than the use of methylphenidate in adolescents and adults with ADHD.	Among 13,863 notifications, 221 cases of psychosis with the use of methylphenidate were found. Secondary analyses showed a persistent overall association between amphetamine use and psychotic symptoms compared with methylphenidate use for reporting subgroups between 13 and 35 years. No reports of the risk of psychosis were found in the 36 to 45 years and 46 to 65 years age groups.
Touafchia et al., 2020	10.1002/hup.2734	Drug-induced tics: An observational postmarketing study	The aim of this study was to investigate the association between tics and drug exposure through a two-step analysis in two pharmacovigilance databases	Psychostimulants were the most associated with tics, especially methylphenidate. The results obtained from the French Pharmacovigilance Database and Vigi Access confirmed the potent association between the use of methylphenidate and tics, with one third of the severe cases found not recovered.
Ekhart et al., 2021	10.3389/fpsyt.2021.692568	Drug-Induced Stuttering: Occurrence and Possible Pathways	The aim of the present study was to detect drugs that have been associated with stuttering and discuss the mechanisms involved.	From VigiBase data associated with stuttering drugs, the 20 main drugs associated with this ADR were obtained, including methylphenidate. Methylphenidate was found in 54 reports, with an ROR of 8.1, so stuttering was considered significantly associated.

Source: Authorship (2024).

Chart 1 above shows the characterization of the studies selected for this literature review, with a detailed approach.

In the study conducted by Wei W et al. (2023), signs of adverse reactions related to psychotic effects were observed in individuals using Methylphenidate, which were related to suicide. They point out that signs of self-destructive behavior in patients aged 19 years and over were the most present, however, signs such as complete suicide, intentional injury and suicidal ideation detected in all age groups were also seen. Hamard J et al. (2024) also identified reports of psychotic symptoms in

patients who took Methylphenidate, although Amphetamines were associated with an even higher number of these symptoms when compared to Methylphenidate in their study. Hollis et al. (2019) challenge the view that Methylphenidate should be avoided in people with psychosis, by comparing data from 12 weeks before and after Methylphenidate treatment, in patients with and without a history of psychosis, and no increased risk of psychotic events was observed.

In addition, another adverse reaction observed during this literature review was dysphemia caused by Methylphenidate. Trenque et al. (2019) identified a sign of Methylphenidate use and speech disorders, especially stuttering, in 13-year-old and male adolescents. Analogous to the previous study, Ekhart et al. (2021) analyzed drug-induced dysphemia, highlighting Methylphenidate as one of the main drugs implicated in this adverse reaction. The study identified mechanisms related to the development of pharmacologically induced stuttering, including the elevation of dopamine levels resulting from the use of Methylphenidate.

The study carried out by Touafchia et al., (2020) relates tics induced by exposure to Methylphenidate as the most frequently associated drug. This frequency was due to the investigation of adverse reactions, in which it was observed that the main suspected class is psychostimulants, with Methylphenidate in approximately 19.8% of the total cases. These data are consistent with those available in VigiAccess, because according to global data within the scope of the International Drug Monitoring Program of the World Health Organization of suspected adverse drug reactions 19, nervous system disorders were reported in 10% of the cases, of which 58 were notifications for movement disorders, bringing this effect as adverse to Methylphenidate. In addition, these data are evidenced by the contraindication of Methylphenidate Hydrochloride in case of diagnosis or family history of Tourette's syndrome.

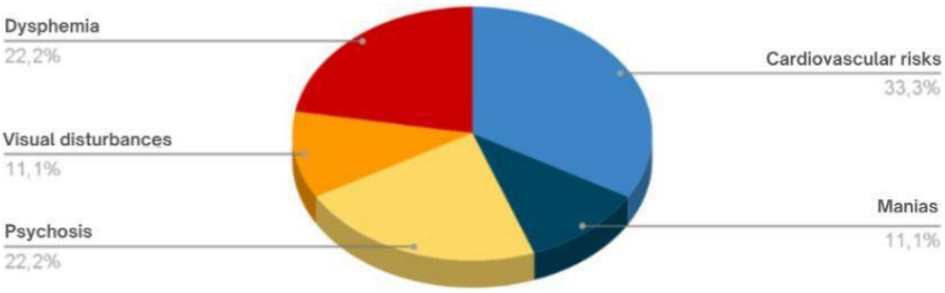
The classification of adverse reactions depends on several factors, and serious ones can result in significant damage and hospitalization, endangering the patient's life. Touafchia et al., (2020) brought data regarding the evolution of these reactions considered serious, which ranged from more than 6 months for the recovery of patients and cases that were not recovered, from the first interruption or reduction of the use of the drug.

Among the adverse reactions listed in the methylphenidate monograph are visual disturbances, including dry eyes, mydriasis, accommodation disturbances, and blurred vision. Soyer et al., 2019, through a case study, reports the occurrence of visual acuity in a child with ADHD being treated with two psychostimulants, including controlled-release methylphenidate hydrochloride. This adverse effect leads to a decline in visual acuity, and is a potential adverse effect of psychostimulant use. After stopping the drugs, the child's vision was restored, evidencing the possibility that this adverse reaction is associated with the use of the drug, which according to Naranjo's algorithm had a score of 10, being classified as a defined adverse reaction. Data present in VigiAccess denote that eye disorders are present in 1% of notifications, consistent with the study by Kleiber et al., (2019) who characterize this effect as defined and uncommon.

In addition to the above, another adverse reaction observed in the findings was the cardiovascular risk that Methylphenidate presents to the patient. Wei W et al., (2023) evidenced in their study symptoms of myocardial infarction and ischemic heart diseases in patients aged 6 to 12 years. In agreement with the study by Montastruc et al., (2022), found in their sample 28% of cases associated with cardiac and/or cardiorespiratory arrests, in this study the age group that primarily presented fatal results was 12 to 17 years. Dubrall et al., (2021), identified potential cardiovascular risks related to the use of methylphenidate, the study examined the European database of adverse drug reactions (ADR) EudraVigilance, which found that the administration of methylphenidate was associated with the onset of tachycardia in patients.

Analysis of studies showed a range of adverse reactions related to the use of methylphenidate. Thus, these reactions can be examined based on the frequency with which they are reported in the studies, as illustrated in Graph 2, below:

Graph 2 - Graph according to the adverse effects most cited in the analyzed articles.



Source: Authorship (2024).

In the graph presented above, it is possible to visualize the adverse effects analyzed in the articles. Among these effects, dysphemia, psychosis, mania, visual disturbances and cardiovascular risks stand out, the latter being the most common. In this sense, visual disturbances and manias were less evident, as they were mentioned in smaller quantities in the selected studies.

4. Conclusion

By reviewing the selected studies, a wide variety of adverse effects that methylphenidate can cause to users were found. Therefore, effects such as cardiovascular risks, growth retardation, tics, visual disturbances, speech alterations, and others related to psychotic effects may be present, impacting the quality of life of those who use it.

For future research, it is recommended, to investigate, the underlying pathophysiological mechanisms that lead to the emergence of these reactions, in different age groups and comorbidities. In addition, longitudinal studies and multicenter research are essential to evaluate the long-term adverse effects of methylphenidate, contributing to the development of safer and more effective therapeutic guidelines.

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