Prevalence of Headache Due to the Use of Methylphenidate: A Systematic Review

Luís Eduardo Teixeira Santos Santana
6rd year Medical Student, Bahiana School of Medicine, Salvador, Bahia, Brazil

Patricia Ramos Borges Ferracioli
Pathologist doctor, Santo Amaro Hospital, José Silveira Foudation, Salvador, Bahia, Brazil

Wagner Ramos Borges
Professor adjunct Bahiana School of Medicine Salvador/Bahia; PhD in Medicine and Health, Bahia Federal University; Vascular surgeon, Member of Brazilian Society of Angiology and Vascular Surgery and Brazilian College of Surgeon, Salvador, Bahia, Brazil

Abstract

Introduction: Attention Deficit Hyperactivity Disorder (ADHD) is a disease that affects the functional and neurological development of individuals and is characterized by hyperactivity and impulsion, it is present in 5% of children and 2.5% of adults across the globe. Its treatment is carried out with methylphenidate which improves the clinical condition of individuals, but this medication also has adverse effects, and in this study we evaluated the headache associated with this medication. Objective: The aim of this study is to define, through an analysis of the literature, the prevalence of headache in methylphenidate users. Methods: A systematic review was conducted with searches on PUBMED and SCIELO. The terms were adapted according to the research platform used, whose combinations involved the following descriptors: “attention deficit disorder with hyperactivity”; “methylphenidate” and “headache”. The study included randomized clinical trials; studies conducted in humans; studies that analyze headache as a side effect of using methylphenidate; studies carried out in the last 10 years. Results: Of the 44 articles identified, five were included for analysis, totaling 593 participants, with a male predominance. The prevalence of headache ranged from 4.3% to 19.5%, higher than the population that does not use methylphenidate, which reinforces the need to monitor, diagnose and intervene on possible negative impacts of headache caused by methylphenidate. Conclusion: The prevalence of headache resulting from the use of methylphenidate ranged from 4.3% to 19.5%. It is also said that there are few studies that associate headache and methylphenidate. The proportion in which the headache appears in patients using methylphenidate, varies according to the presentation of the drug.

Introduction

Attention Deficit Hyperactivity Disorder (ADHD), is found in approximately 5% of children and 2.5% of adults in all cultures [8], is associated with functional impairment in these individuals and their neurological development, generally presenting, with hyperactivity and impulsion. And, currently, the drug of choice for its treatment is methylphenidate, which has become the most consumed psychostimulant in the world, surpassing all others combined [10,11], it works by improving attention, concentration and consequently the performance of patients [1,2], and, Due to this characteristic, it is also used in a non-prescribed manner by a portion of the population that aims to improve concentration and memory, whether they are participants in public competitions, even pre-university students or universities [9]. Despite the benefits present, users report some uncomfortable symptoms when using it. In a study published by COCHRANE LIBRARY, difficulty falling

More Information


DOI: 10.59324/ejmhr.2023.1(3).04

Keywords:
Prevalence, methylphenidate, ADHD, Attention deficit hyperactivity disorder, headache.
asleep was identified in 17.9%, abdominal pain in 10.7%, decreased appetite in 31.1% and, the symptom studied in this work, headache, which presented numbers of 14.4% [1]. The latter has important impacts on patients’ lives, whether in the fear of using the medication, and consequent poor adherence, or in the discomfort caused by pain [1,2].

Despite this, there are few studies that address headaches resulting from the use of methylphenidate, which makes it difficult to elucidate its prevalence among methylphenidate users. The insufficiency of these studies is highlighted in both Brazilian and international literature.

Given the use of methylphenidate by people with ADHD and by an unknown portion that uses it in a non-prescribed way, we see a need to research and publicize the relationship between headache and methylphenidate, so that it does not become a public health problem, generating greater security and knowledge for doctors who prescribe and comfort and confidence for those who use this medication as prescribed [9].

**Pharmacology of Methylfenidate**

Methylphenidate is a medication that belongs to the therapeutic group of psychostimulants of the central nervous system, it is sold in Brazil as Concerta®, Ritalin® and Ritalin LA® [12]. And it is prescribed based on the yellow recipe (A3). This medication is only indicated for the treatment of Attention Deficit Hyperactivity Disorder and for the treatment of narcolepsy. [12]

It is a racemic mixture composed of d and l isomers, with the disomer being more active than the l isomer. Current science demonstrates that methylphenidate binds to dopamine-rich areas in the brain, the main sites being the prefrontal cortex, a region shown to play a prominent role in the pathophysiology of ADHD [4]. Its mechanism of action is still unclear, but methylphenidate has been shown to act by inhibiting the reuptake of norepinephrine and dopamine, which prolongs the action of these neurotransmitters. At higher doses it increases norepinephrine and dopamine efflux throughout the brain, which can result in impaired cognition and locomotor activation effects; on the other hand, at lower doses it selectively activates norepinephrine and dopamine neurotransmission in the pre-neurocortical cortex. Frontal, an important area of attention, maximizing clinical effectiveness and preventing side effects [4,5]. Thus, for the treatment of ADHD, lower doses are used, which reduce locomotor agitation, impulsivity and increase cognitive function, including sustained attention and working memory [6]. There are currently three hypotheses regarding the role of alpha-adrenergic receptors in ADHD. The first of them suggests that the cerulean locus plays an important role in attention, and that it has a vast number of alpha-adrenergic receptors, so if there is dysfunction in these receptors, the cerulean locus would react to any stimulus and would not maintain sustained attention to just one stimulus [4,5]. The second hypothesis states that the noradrenergic fibers coming from the locus coeruleus towards the superior parietal cortex are essential to maintain the function of this cortex and thus provide attention, so the dysfunction of this brain region would explain ADHD [6]. The third hypothesis states that noradrenergic neurons in the prefrontal cortex stimulate this region, acting in a regulatory manner, inhibiting irrelevant stimuli and restricting hyperactive behaviors. Therefore, its dysfunction would imply difficulty in attention [7].

**Attention Deficit/Hyperactivity Disorder**

Based on the DSM-V, ADHD involves 5 diagnostic criteria. For criterion A, a persistent pattern of inattention and/or hyperactivity-impulsivity is required that interferes with the functioning and development of the individual, whose inattention is characterized by not paying attention to details or making careless errors in school tasks, difficulty maintaining attention to tasks or recreational activities; not following instructions to the end and failing to complete school work, chores or workplace duties; difficulty organizing tasks and activities; avoids, dislikes or is reluctant to engage in tasks that require prolonged mental effort, among other characteristics. While hyperactivity-impulsivity is characterized by a patient who fidgets in the chair, taps feet and hands, gets up from the chair, runs or climbs on things at inappropriate times, is unable to carry out leisure activities clearly, talks too much, among others. Other symptoms. For criterion B, a large amount of inattention or hyperactivity-impulsivity symptoms should exist before the age of 12. In criterion C, a large number of the symptoms must be present in two or more environments. To fulfill criterion D, there must be evidence that the symptoms interfere with social, school or professional functioning or that it impairs its quality. And in criterion E, the symptoms must not occur exclusively during schizophrenia or another mental disorder [8].

**Side Effects Resulting from the Use of Methylfenidate**

Studies around the planet indicate that ADHD occurs in most cultures with a prevalence of 5% in children and 2.5% in adults. And its first-line treatment is carried out with the active substance, methylphenidate (MPH), it has been shown that MPH exhibits its therapeutic response in approximately 70% of patients, although it also has several known side effects, there are few studies that examine these effects. Lee J. et al. observed in their study a profile of side effects that is characterized by an increase in the frequency and severity of insomnia, reduced appetite, headaches and stomach pains when compared to patients using placebo [2].
In the study by Lee J. et. al. [2], a correlation was made between the use of MPH and the side effects that manifested during the therapeutic response and it took into account the parents' judgment by SERS and CGI-P. In this work, the interesting thing was that the most frequent side effects, insomnia, reduced appetite and headaches, did not demonstrate any significant correlation. And they believe that parents are influenced by effects such as the propensity to cry, irritability and anxiety in their judgment of behavioral improvement [2].

Jafarinia M. et al. [3] carried out a randomized, double-blind clinical trial, comparing bupropion and methylphenidate in the treatment of ADHD, between 2010 and 2011. As a result, they found no significant differences between parental assessments between the two groups. Similar results were obtained when inattention and hyperactivity were compared between the two groups. Eleven side effects were recorded during the course of the study; however, no serious adverse events were observed in any of the patients. The most common effects were decreased appetite (55%), insomnia (50%), and headache (50%) in the methylphenidate group and decreased appetite (45%) and insomnia (35%) in the bupropion group. Ten (50%) patients in the methylphenidate group and three patients in the bupropion group (15%) experienced headache.

Methodology

Searches in electronic data sources MEDLINE/PubMed, Embase, The Cochrane Library, CINAHL, Web of Science, Scopus and Biblioteca Virtual em Saúde (VHL) were carried out using a combination of descriptors, including terms from the Medical Subject Headings (MeSH), Health Sciences Descriptors (DECs) and descriptor contractions. The systematic review was not restricted to publications in English, as studies written in Portuguese were also included. The PRISMA protocol was used as a guide for the systematic review. The terms used for the search were related to the population analyzed (MeSH Term: attention deficit disorder with hyperactivity), the drug under investigation (MeSH Term: methylphenidate) and the side effect caused (MeSH Term: headache). References present in the articles identified by the search strategy were also searched manually in order to add to the work and literature review. The final combination of descriptors was ((attention deficit disorder with hyperactivity) AND (methylphenidate)) AND (headache).

The inclusion criteria were: randomized clinical trials, clinical trials, community trials in which an intervention group is compared to a control group; studies conducted on humans; studies that analyze headache as a side effect of the use of methylphenidate; studies carried out in the last 10 years.

The exclusion criteria were: studies whose patients used other drugs; studies with a low level of quality; animal studies; interventions lasting less than 4 weeks; letters, abstracts, conference proceedings, observational and conglomerate studies. Two pairs of independent authors separately read the titles and abstracts of each pre-selected work, in order to identify only the studies that correctly met the inclusion criteria. The articles continued to be read separately by 2 authors, in order to ensure the systematic review criteria. Any disagreements between the authors were resolved through discussion and dialogue, in the presence of a third author.

Two authors collected the data using a pre-defined collection form. The characteristics of the extracted studies included: publication date, geographic origin, title, study definition, intervention duration, supervision, financing, among others. Data were recorded about the participants in each work, number of participants, gender, age, ethnicity, type of ADHD. Finally, data on the prevalence of headaches before and after the intervention were collected, with the respective variances.

The quality of each study was assessed using the Cochrane Tool for Assessing Risk of Bias, which contains the following criteria: adequate randomization; participant allocation; blinding of participants, blinding of the results assessor; integrity of results, incomplete data; selective reporting of results; and other sources of bias (e.g. effect of small studies).

Results

Initially, 44 studies were identified in bibliographic searches in the Pubmed and NCBI databases. After being subjected to the inclusion and exclusion criteria, eleven studies were selected. After complete reading, 5 articles were included following the inclusion and exclusion criteria of this systematic review.

Five studies were selected that evaluated the clinical and demographic profile of ADHD patients using methylphenidate. The Articles were produced in the United States, 2 of which were designed by Wigal SB, in the United States, in 2012 and 2013. In these studies, for the diagnosis of Attention Deficit/Hyperactivity Disorder, the criteria of the International Classification of Diseases 10th edition were adopted (ICD-10) and Diagnostic and Statistical Manual of Mental Disorders IV or V (DSM IV/DSM V). All articles are randomized clinical trials.

The characteristics of the selected studies indicated that the studies were predominantly carried out in the United States, being published in international journals. Regarding sample sizes, they presented quantitative variations, Wigal, SB (2013) used 44 participants while Findling, RL (2010) used 217 participants. In relation to socio demographic factors, in the work of Wigal, SB (2013), the average age was 8.8 years, while in the work...
of Findling, RL (2010), the average age was 14.6, generating a difference. Among the age groups, in the first the average age group is children while in the second there is a prevalence of teenagers, leaving room for divergences. The ethnicity of the participants was also assessed, with the highest prevalence being White, followed by Black/African-American and without a large number of other ethnicities. The majority of participants were male in all research. The most prevalent type of ADHD was combined (Inattention with Hyperactivity).

Regarding the prevalence of headache, the work by Wigal, SB [13] found a prevalence of 8.9% in the intervention group. In the works of Childress [14], 19.5% were found. In the study carried out by Brams [15], the values found were 4.3% in the methylphenidate group. In Wigal’s second work [16], the prevalence of headache was 17.8%. And in the clinical trial carried out by Finding [17], headache was present in 12.4% of participants using methylphenidate. The only study that presented data regarding headache in the placebo group was the one carried out by Brams [15], whose values were found to be 1.9% in the placebo group.

This assessment was carried out using the Cochrane tool. It is a two-part tool, addressing the six specific domains (sequence generation, allocation concealment, masking, incomplete outcome data, selective outcome reporting, and ‘other issues’). The first part of the tool involves describing what was reported to have happened in the study. The second part of the tool involves assigning a judgment related to the risk of bias for that input. This is achieved by answering a pre-specified question about the appropriateness of the study in relation to the input, such that a judgment of ‘Yes’ indicates low risk of bias, ‘No’ indicates high risk of bias and ‘Not clear’ indicates risk clear or unknown bias.

After taking into account additional information provided by study authors, studies were grouped into the following categories.

**Discussion**

In this systematic review, a total sample of 593 Methylphenidate users was evaluated, and the prevalence of headache among them was observed, which ranged from 4.3% to 19.5% in the studies evaluated. This result is relevant when compared to global literature, where rates vary according to etiology, with the most documented being migraine headache, tension headache and chronic daily headache. And, it is known that, for the general population, the total prevalence of headache reaches 46%, however, when divided according to its cause these numbers reduce, chronic daily headache, for example, affects 3% of the population across the globe [19].

Stovner et al. [19], carried out an estimate in countries distributed across all continents of the world, and in a review of 107 epidemiological studies, he states that the average frequency of headache in general was 46%, 11% for headache migraine, 42% for tension headache, and 3% for chronic daily headache. Queiroz and Silva Junior [18], evaluated 6 epidemiological studies of headache in Brazil, and found an average prevalence of 70.6% of headache in general, 15.8% of migraine, 29.5% of tension headache and 6.1% of headache chronic daily.

Brams et al. [15], carried out a crossover study comparing different concentrations of MPH tablets in 157 children diagnosed with ADHD based on DSM-IV criteria, for the study children aged 6-12 years were selected, 2 weeks before they were previously stabilized with methylphenidate, after that, randomized to receive Dexmethylphenidate (slow-release methylphenidate) 20 mg/day, 30 mg/day or placebo for 7 days each, the scheme was 3 drugs for a period of 3 weeks, and the prevalence found for headache it was 4.3% in the period in which patients were using medication, whereas when they used placebo the number fell to 1.9%. Wigal et al. [13] tested the efficacy and safety of MPH in the form of a chewable tablet and found 8.9% of headaches.

The research was carried out on 85 children aged 6 to 12 years with a diagnosis of ADHD determined by an appropriate doctor, using 3 criteria as a basis, the K-SADS, the CGI-S and the ADHD-RS-IV and included a 6-week, open, dose optimization treatment period, followed by a randomized, double-blind and placebo-controlled. The dose administered to patients varied from 20 mg to 60 mg per day. Additionally 81% of participants had no exposure to MPH or dexmethylphenidate hydrochloride within 1 month prior to screening. In the work of Findling et al [17], who evaluated an ADHD treatment system with transdermal methylphenidate compared to transdermal placebo, they found a frequency considerably higher than the previous ones, with a percentage of 12.4%. In this work, 217 adolescents from 7 at 17 years old diagnosed with ADHD according to DSM-IV, the duration of medication use was 7 weeks. For Wigal et al. [16], who evaluated the efficacy of NWP06, a prolonged release liquid formulation of MPH, the results were 17.8% different. A placebo-controlled crossover was carried out in which 45 patients were between 6 and 12 years old and were diagnosed with ADHD, in this study there was an open phase to optimize the dose (4-6 weeks) and a crossover phase (1 week placebo x 1 week MPH) lasting 8 weeks.

Childress and collaborators [14] found the highest numbers of headaches among the studies evaluated in this systematic review 19.5%, their work evaluated the effectiveness of an innovative formula, an orally...
disintegrating tablet, in 87 children aged 6 to 12 years diagnosed with DSM-IV ADHD, in this study eligible patients should have already used the MPH for at least 1 month before screening. The randomized clinical trial was placebo-controlled, and divided into 5 periods (screening, cleansing, dose optimization, stabilization and the placebo x MPH phase) and the time of using the drug was only 5 weeks. Comparing the results of the studies included in this systematic review, the hypothesis that there is a significant relationship between the use of methylphenidate and headache is reinforced. Furthermore, it is possible to state that the time of exposure of users to the drug does not affect the number of patients with this adverse effect, as in the lowest numbers patients were exposed for 3 to 6 weeks to the drug, while in the highest result patients had 5 weeks of contact. Furthermore, it is also concluded that the form of administration contributes to the frequency of the symptom, as the oral tablet presented the lowest numbers, while a liquid formulation and an orally disintegrating tablet occupied the top of the table. The demographic variables assessed by Brams et al. [15] were sex, race, diagnosis of ADHD in the DSM-IV, weight, height and duration of symptoms. The average age of all randomized patients was 9.6 years. and the average height and weight measurements of this population were 138.5 cm and 37.3 kg, respectively. Patients were predominantly of white (38.2%), black (31.5%), or Hispanic (22.4%) ethnicity. The average duration of ADHD symptoms was 5.2 years, and there were slightly more men (57%) than women (43%), and the prevalence found for headache was 4.3%. In the work of Wigal et al.13, for the group using MPH, the demographic variables evaluated were gender, 71.4% male and 28.6% female, age, whose average was 9.9 years, race, in which the majority were white (64.3%) and black (28.6%) and the type of ADHD in which those with inattention were 28.6% and those with inattention and hyperactivity 71.4%.

Findling et al. [17], worked with patients with an average age of 14.3 years, in which 74.7% of participants were men, 77% were white and 18.4% black. In the research by Wigal et al.16, the majority of participants were white (80%), male (73%) and were not of Hispanic/Latino ethnicity (75%). The average age was 8.8 years and presented a normal distribution. All types of ADHD (inattentive, hyperactive/impulsive, and combined) were represented, and the majority of individuals (71%) were diagnosed with the combined type. In the work of Childress et al. [14], of the 87 participants, 74.7% were diagnosed as the combined type of ADHD, 24.1% as the predominantly inattentive type and 1.1% as predominantly hyperactive/impulsive. The majority were male (65.9%), white (79.3%), and non-Hispanic/Latino (65.9%). The average age was 9.2 (1.75) years and the body mass index was 18.5.

Analyzing the sociodemographic data, it was observed that the research that found the lowest frequency for headache is the one that presents the greatest balance of gender (men and women) and ethnicity (blacks, whites and Hispanics), while in the other studies the number of men was much higher, as well as that of white participants, however, due to the different MPH administration formulas in the studies, it cannot be said that the prevalence of headache is higher in male and/or white patients, and thus it is evident the need to carry out new research to elucidate this information. This work analyzed results of research involving the drug methylphenidate, consequently the studies found are those available in the literature, and all of them were carried out with the population of the United States of America, which is a limitation for the results, as the risk of bias. Furthermore, research did not reveal the prevalence of headache prior to treatment with methylphenidate, which makes it difficult to analyze the results. Another factor that raises questions is the use of different presentations of the medication between the studies, that is, there was no standard dosage, route of administration or release time of the medication in the body, factors that can interfere with the side effects of the medications.

Conclusion
At the end of this systematic review, it was concluded that the prevalence of headache varies from 4.3% to 19.5%, the total sample was 593 Methylphenidate users. It was also found that the different forms of administration of Methylphenidate contribute to the variation in the number of patients affected by headache. In order to elucidate the profile of patients affected by headache resulting from the use of methylphenidate, it is necessary to carry out more studies on the subject, mainly in samples outside the United States.

Financial support:
None.

Conflicts of interest
No conflicts of interest declared concerning the publication of this article.

References

ADHD. BMC Psychiatry. 2011 Apr 21;11:70. doi: 10.1186/1471-244X-11-70


