Research, Society and Development, v. 13, n. 10, e11131046967, 2024
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v13i10.46967

Adverse effects resulting from the use of zolpidem hemitartrate: A literature review

Efeitos adversos resultantes do uso do hemitartarato de zolpidem: Uma revisão da literatura

Efectos adversos derivados del uso de hemitartrato de zolpidem: Una revisión de la literatura

Received: 09/17/2024 | Revised: 09/30/2024 | Accepted: 10/01/2024 | Published: 10/05/2024

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Abstract
Objective: To investigate and discuss the risks associated with the use of the drug in order to clarify the possible damage to health. Methods: Through an integrative review, using the guiding question "What are the main adverse effects and impacts of using zolpidem?". The search was carried out in the main databases: Latin American and Caribbean Health Sciences Literature (LILACS), Medical Literature and Retrieval System onLine (MEDLINE/PubMed®), Periódicos CAPES and Scientific Electronic Library Online (Scielo). MESH (Medical Subject Headings) and DeCs (Health Sciences Descriptors) were used as descriptors in the search strategy. The search strategy followed the criteria of the Boolean operator "AND", which combines terms. The terms used were zolpidem "AND" adverse effects AND overdose, during the month of September 2024. Results: Zolpidem is a drug of paramount importance for the treatment of cases of insomnia, and long-term medical therapy should be monitored to assess efficacy, the emergence of adverse effects and the onset or worsening of comorbid conditions. Conclusion: Strict prescription control and continuous evaluation of its impact on patients' physical and mental health are essential to avoid abuse and serious complications.
Keywords: Zolpidem; Adverse effects; Overdose.

Resumo
Objetivo: Investigar e discutir os riscos associados ao uso do medicamento para esclarecer os possíveis danos à saúde. Métodos: Por meio de uma revisão integrativa, utilizando uma questão norteadora "Quais são os principais efeitos adversos e impactos do uso do zolpidem?". A busca foi realizada nas principais bases de dados: Literatura LatinoAmericana e do Caribe em Ciências da Saúde (LILACS), Medical Literature and Retrieval System onLine (MEDLINE/PubMed®), Periódicos CAPES e Scientific Electronic Library Online (Scielo). MESH (Medical Subject Headings) e DeCs (Descritores em Ciências da Saúde) foram usados como descritores na estratégia de busca. A estratégia de pesquisa seguiu os critérios do operador booleano "AND", que combina termos. Os termos usados foram zolpidem "AND" adverse effects AND overdose, durante o mês de setembro de 2024. Resultados: O zolpidem é um medicamento de suma importância para o tratamento de casos de insônia, e a terapia médica de longo prazo deve ser

monitorada para avaliar a eficácia, o surgimento de efeitos adversos e o aparecimento ou agravamento de condições comórbidas. Conclusão: O controle rigoroso da prescrição e a avaliação contínua do seu impacto na saúde física e mental dos pacientes são essenciais para evitar abusos e complicações graves.
Palavras-chave: Zolpidem; Efeitos adversos; Superdose.

Resumen
Objetivo: Investigar y discutir los riesgos asociados al uso del medicamento para esclarecer los posibles daños a la salud. Métodos: A través de una revisión integradora, utilizando como pregunta orientadora "¿Cuáles son los principales efectos adversos e impactos del uso de zolpidem?". La búsqueda se realizó en las principales bases de datos: Latin American and Caribbean Health Sciences Literature (LILACS), Medical Literature and Retrieval System onLine (MEDLINE/PubMed®), Periódicos CAPES y Scientific Electronic Library Online (Scielo). Se utilizaron MESH (Medical Subject Headings) y DeCs (Descriptores en Ciencias de la Salud) como descriptores en la estrategia de búsqueda. La estrategia de búsqueda siguió el criterio del operador booleano «AND», que combina términos. Los términos utilizados fueron zolpidem «AND» efectos adversos AND sobredosis, durante el mes de septiembre de 2024. Resultados: El zolpidem es un fármaco de suma importancia para el tratamiento de los casos de insomnio, y el tratamiento médico a largo plazo debe ser monitorizado para evaluar la eficacia, la aparición de efectos adversos y la aparición o empeoramiento de condiciones comórbidas. Conclusión: El control estricto de la prescripción y la evaluación continua de su impacto en la salud física y mental de los pacientes son esenciales para evitar el abuso y las complicaciones graves.
Palabras clave: Zolpidem; Efectos adversos; Sobredosis.

1. Introduction

Anxiety and sleep disorders are recurrent complaints in health services. Sleep quality and quality of life are closely related. Stress and worry increase sleep latency and nocturnal awakenings, and poor sleep quality leads to consequences in everyday life (Arnts et al., 2024). Some changes in habits can improve sleep quality. A hypnotic drug should produce drowsiness and stimulate the onset and maintenance of a state of sleep, and various drugs have been used to generate sleep, which have subsequently been replaced by safer and more effective options (Zhong et al., 2024).

According to the World Health Organization (WHO), a large proportion of the Brazilian population reports suffering from a sleep disorder. When there is no effective response to the disorder from non-pharmacological treatment, pharmacological treatment is indicated. The use of pharmacological treatment for insomnia is increasing significantly nowadays, but there are many adverse effects, and a careful assessment of the benefit-risk ratio is necessary (Lima et al., 2024). Considered to be a drug widely prescribed for the treatment of transient or chronic insomnia, zolpidem, which belongs to the non-benzodiazepine hypnotics group, is also called Z-drugs or Z-hypnotics in the literature. It is derived from imidazopyridines and has a depressant action on the central nervous system (Inoue et al., 2023). The forms marketed are: tablets, extended-release tablets, sublingual tablets and oral spray, with various brands registered with the National Health Surveillance Agency (ANVISA, 2024; Yu et al., 2024).

This hypnotic effect of zolpidem is related to its agonist interaction with GABA A receptors, chloride channels that promote the depression of neuronal transmission, which in turn reduces sleep latency and increases its duration are expected effects. However, as with any medication that depresses the central nervous system (CNS), there are adverse effects that may or may not appear, such as drowsiness, headaches, dizziness, exacerbated insomnia, double vision, loss of balance, sleepwalking and disorders such as anterograde amnesia, which results in the patient's vulnerability (Castro et al., 2019; Oliveira Azevedo et aol., 2022).

Ordinance 344, instituted in 1998 by the Ministry of Health, regulates the prescription and control of narcotic and psychotropic substances. Until recently, this provision allowed Zolpidem to be widely prescribed for the treatment of insomnia in drug preparations of up to 10 mg, as it was classified under Addendum 4 of the B1 list - a prescription with a low level of control. However, the drug became increasingly popular due to its ease of access, and news outlets began to denounce the adverse effects and risks related to abuse of this drug (Medicina S/A, 2021). Public concern about the safety of this drug and the fuss

about the potential for a public health problem had repercussions on the Ministry of Health, which decided to exclude Addendum 4 from the B1 list in order to increase the strictness of prescribing this drug and restrict access by classifying it on the B2 list with a high level of control and monitoring of disposal and use. (Moorthy et al., 2024).

Therefore, as the potential for abuse of Zolpidem is significant (Zhong et al., 2024), especially at high dosages or for long periods of time - it is safe to say that increased control of the drug is important in order to reduce the risk of abuse risks to public health (Castro et al., 2019). Therefore, this measure implies effective prevention against indiscriminate use and reduces the occurrence of serious adverse effects with a guarantee of safer and more appropriate use.

Therefore, despite the need for adequate sleep being fundamental to maintaining human health, care must be taken when using drugs such as Zolpidem. This is because adverse effects such as parasomnias and anterograde amnesia affect around 15% of patients (Westermeyer et al, 2020) and are just some of the reactions associated with the use of this drug, which has become popular in recent years. It is therefore important to investigate and discuss the risks associated with the use of the drug in order to clarify the potential damage to health.

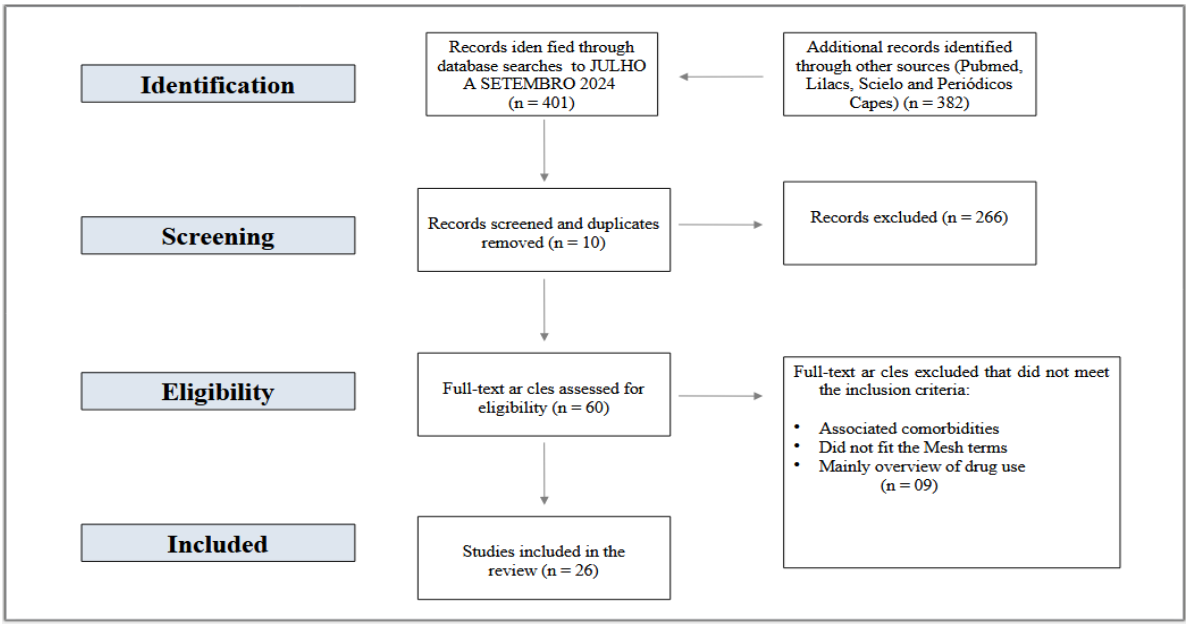
2. Methodology

An integrative review was carried out according to Snyder, H. (2019) with the formulation of the research question, the elaboration of strategies with the objective of finding the necessary data to integrate the results, using a guiding question "What are the main adverse effects and impacts of the use of zolpidem?". The search was carried out in the main databases: Latin American and Caribbean Health Sciences Literature (LILACS), Medical Literature and Retrivial System onLine (MEDLINE/PubMed®), Periódicos CAPES and Scientific Electronic Library Online (Scielo). MESH (Medical Subject Headings) and DeCs (Health Sciences Descriptors) were used as descriptors in the search strategy.

The search strategy followed the criteria of the Boolean operator "AND", which combines terms. The terms used were zolpidem "AND" adverse effects AND overdose, during the month of September 2024.

The following inclusion/exclusion criteria were used: studies with free access, available online, complete, in English/Portuguese/Spanish, published between 2019 and 2024, and those that did not fit the above descriptions were excluded.

Figure 1 - Selection flowchart of articles included in the review.



Source: Authors (2024).

3. Results and Discussion

Zolpidem is a drug of paramount importance for the treatment of cases of insomnia, and long-term medical therapy must be monitored to assess efficacy, the appearance of adverse effects and the onset or worsening of comorbid conditions (Edinoff et al, 2021).

The search for articles resulted in 382 articles, of which 266 were excluded because they did not fit the criteria, 60 were selected by reading the title, then the abstract and, finally, 26 were selected and read in full and included in this review. Of these articles, 14 constitute a campus sample, as shown in Table 1.

Table 1 - Description of the studies found on zolpidem and its adverse effects, databases where they were found, highlighting the objectives and general considerations of the text.

AUTHOR/YEAR	ARTICLE TITLE	DATABASE	ARTICLE OBJECTIVES	MAIN CONCLUSIONS OF THE TEXT
Amari et al., (2022)	Falls, healthcare resources and costs in older adults with insomnia treated with zolpidem, trazodone, or benzodiazepines	PubMed	To carry out a retrospective cohort study from January 2011 to December 2017 based on administrative data from medical services, considering patients over 65 with insomnia who receive medication for this condition, with the aim of evaluating the incidence of falls, hip fractures and traumatic brain injury.	Patients who received pharmacological treatment for insomnia had a substantially higher rate of comorbidity. Patients taking benzodiazepines had more than one episode of falls in 11.3%; those taking trazodone, 9.5%; immediate-release zolpidem, 7.7%; slow-release zolpidem 6%; and the control group 3.1%.
Zhou, Liu, Tang e Tang, (2023)	Effects of new hypnotic drugs on cognition: A systematic review and network meta-analysis	PubMed	To assess whether different doses of hypnotic drugs, such as DORA and Z drugs, induce cognitive impairment.	In the long term, DORA is the drug with the best intervention for insomnia, since it was the most effective in maintaining sleep, while Zolpidem, even though it had a prolonged effect on maintaining sleep, had considerable effects on cognition when administered in the long term.
Edinoff et al., (2021)	Zolpidem: Efficacy and Side Effects for Insomnia	PubMed	Analyze the adverse effects following the use of Zolpidem for the treatment of insomnia.	A careful analysis of whether or not to prescribe Zolpidem to patients suffering from insomnia is essential. Clinical monitoring of patients using this medication is essential due to the serious effects associated with it, such as sleepwalking, risk of falls and seizures.
Ferenidou, Mourikis, Sotiropoulou e Vaidakis, (2019)	Zolpidem related persistent genital arousal disorder: An interesting case	PubMed	To highlight the need for more research into the factors that contribute to the development of persistent genital arousal disorder, with a focus on the possible link between the use of zolpidem and the onset of this condition	The article points out that this association is not yet widely reported in the literature, suggesting the importance of future research to improve the understanding and treatment of persistent genital arousal disorder (PGED).
Husnain, Qadeer, Tanvir e Nadeem, (2024)	Zolpidem's insidious potential of abuse: A word of caution	PubMed	To warn about the side effects and risks of zolpidem use, the adequacy of current laws and regulations to protect the public from zolpidem abuse and its harmful effects, and to suggest the need to increase public and professional awareness of the dangers of zolpidem.	Although initially considered safe, studies associate zolpidem with complex behavior during sleep, euphoria, addiction and even suicide. The text therefore warns of inadequate regulation in countries such as Pakistan and calls for awareness and stricter laws to control over-the-counter use. France is cited as an example of effective action against abuse.

Westermeyer e Carr, (2020)	Zolpidem Associated Consequences An Updated Literature Review With Case Reports	PubMed	To carry out a retrospective literature review after the year 2000, based on data available on PubMed on medical problems associated with zolpidem, such as cases of hallucinations and delusions, and epidemiological prevalence rates, analyzing, through two case reports, the impacts of these effects as an international pandemic of preventable health problems.	In the cases exposed in which Zolpidem and antidepressants were administered for a week or more, the adverse symptoms related to cases of delirium and hallucinations persisted for up to a month. In addition, the two reports analyzed in the article linked the use of Zolpidem to cases of delirium and acts of violence, such as homicides, reinforcing the need to combat this "pandemic".
Westerlind, Östgren, Mölstad, Midlöv e Hägg, (2019)	Use of non-benzodiazepine hypnotics is associated with falls in nursing home residents: a longitudinal cohort study	PubMed	To investigate the association between the use of certain classes of medication, including non-benzodiazepine hypnotics (zopiclone and zolpidem), and falls in elderly residents of Swedish nursing homes and to relate them to different age groups.	An increased risk of falling was found in 93% of the study subjects (aged between 65 and 101). Regular use of non-benzodiazepine hypnotics was associated with a history of falls and, prospectively, with serious falls in older age groups. These findings indicate the need for greater caution in relation to regular non-benzodiazepine hypnotic therapy for insomnia in elderly people living in care homes, especially among older people.
Schifano, Chiappini, Corkery e Guirguis, (2019)	An Insight into Z-Drug Abuse and Dependence: An Examination of Reports to the European Medicines Agency Database of Suspected Adverse Drug Reactions	PubMed	To prove the direct relationship between the administration of Z medicines and their adverse effects, by analyzing data on adverse reactions, such as dependence and withdrawal, to medicines provided by the European Medicines Agency through the EudraVigilance system.	Zolpidem and zopiclone presented the same risk of dependence, but zopiclone was more involved in adverse reactions related to overdose. Compared to zaleplon, zopiclone presented greater problems related to dependence and overdose. It is therefore clear that caution should be exercised when prescribing these drugs, especially for patients with psychiatric illnesses or a history of drug abuse, so it is essential to invest in proactive pharmacovigilance activities to better understand and prevent any potential misuse of prescription drugs.
Barbosa Eyler e Castro, (2023)	Dependencia y abstinencia de zolpidem. Reporte de un caso de convulsiones generalizadas	Lilacs	Checking zolpidem withdrawal symptoms in a high-dose user patient.	Abruptly stopping zolpidem can lead to abuse of other drugs, addiction and, in more serious cases, seizures, as reported in the case study.
Castro et al., (2019)	Sublingual and oral zolpidem for insomnia disorder: a 3-month randomized trial	Lilacs	To compare the safety and efficacy of two presentations of Zolpidem, the 5 mg sublingual and the 10 mg oral, in a randomized trial.	Both presentations of Zolpidem reduced the number of nocturnal awakenings and increased the hours of sleep, and both have similar safety and efficacy. The sublingual form leads to shorter sleep latency.
Tavares et al., (2021)	Cognitive and balance dysfunctions due to the use of zolpidem in the elderly: a systematic review	SciELO	Carry out a systematic review to analyze the acute effect of different dosages of Zolpidem (5 mg, 6.25 mg, 10 mg and 12.5 mg) on cognition and balance in the elderly.	The analysis found no evidence of cognitive dysfunction in the elderly during the use of Zolpidem, but did find evidence of altered balance.

Mittal et al., (2021)	Zolpidem for insomnia: a Double-edged Sword. a Systematic literature Review on Zolpidem-induced Complex Sleep behaviors	CAPES	Carry out a systematic review on complex behaviors during sleep induced by Zolpidem.	Data from 148 patients was collected from three observational studies. The most common complex behaviors during sleep were sleepwalking and disordered eating.
Joung, (2023)	Gender differences in spontaneous adverse event reports associated with zolpidem in South Korea, 2015–2019	CAPES	To look for evidence of the influence of gender on the adverse effects of Zolpidem from the Odds Ratio calculated from a database of volunteers during the period 2015-2019 in South Korea.	The data analyzed shows differences in adverse effects between genders. Sleepwalking and cardiovascular disorders were more common in females and cognitive effects were more common in males.
Grzegorzewska et al., (2020)	Clinical considerations of sleep related amnestic behaviors associated with zolpidem.	CAPES	To review the most serious adverse effects of Zolpidem. To look for patterns and predisposing factors for side effects by searching the Pubmed and Google Scholar databases.	Zolpidem is effective in treating insomnia, but it can have as many adverse effects as benzodiazepines. Complex behaviors are related to the use of Zolpidem in various literature sources. Risk factors include female gender, somatic comorbidities, use of other sedatives, previous history of abuse of other sedative drugs and use of higher than recommended doses. Patient education and the association with non-pharmacological therapy improve clinical practice.

Source: Authors (2024).

Results were analyzed objectively and subjectively to see how well the drug worked in improving sleep and whether it was safe for clinical use. However, the evidence indicated that Zolpidem is effective in reducing the time it takes to fall asleep and episodes of nocturnal awakening and increasing total sleep time and sleep efficiency (length of time spent asleep compared to time spent in bed) (Castro et al., 2019).

As for safety and tolerance, studies by Machado et al, (2020) show that when dosages and guidelines are respected, there is a low risk of daytime sleepiness and impaired memory or psychomotor performance. However, some retrospective studies have linked Zolpidem to falls, fractures, dementia, cancer and strokes.

A total of 94 adverse effect signals were identified. Of these, 35 signs showed significant disparities between the genders at the 5% level or were observed in only one of the genders. When categorizing adverse effects by similarity, parasomnias such as sleepwalking and nightmares, and cardiovascular problems such as coronary thrombosis, had a higher risk of being reported among women (Zhou et al., 2023). On the other hand, men more often reported cognitive disorders such as delirium, and conditions related to insomnia and movement disorders. Thus, of all the adverse effects with variations in risk between genders, the difference observed in sleepwalking was the most striking and consistent (Grzegorzewska et al., 2020; Joung, 2023).

The literature contains other types of interventions for insomnia problems that can be effective in inducing sleep without harming the cognitive process, such as eszopiclone and zopiclone, which have improved sleep quality, although all drugs still require verification as to their safety margin (Schifano, Chiappini, Corkery and Guirguis, 2019). According to the reading of the articles, the data indicate that there are effects such as food intake events during sleepwalking episodes, as well as euphoria in patients in the case of high doses, adverse events in memory such as amnesia, some articles mention neuroprotective and antioxidant effects in neurodegenerative diseases which could according to the authors have beneficial effects but there are also risks of death due to abusive situations (Medeiros Fernandes et al., 2024).

Zhang et al, (2024) points out that the gradual reduction in the use of zolpidem affects sleep. In their study, the time of

deep sleep in the groups tested was reduced in the first stage, and as treatment continued, this symptom was relieved. In the second stage, prolonged use of zolpidem had a greater effect than in the control group; the upward trend was significant, but differed slightly between the groups.

4. Conclusion

Although it effectively performs its function as a sleep inducer, its effects on the CNS are visible and are not yet fully understood. Further studies into the effects of zolpidem on the CNS are needed. It is possible to conclude that Zolpidem is a useful drug for the treatment of insomnia, but in conjunction with cognitive-behavioral monitoring. However, there are adverse effects such as sleepwalking, amnesia, and even impairment of psychomotor functions, complex behaviors, excessive sleep, and it can also lead to hallucinations, highlighting the need for caution in its use. Strict prescription control and continuous evaluation of its impact on patients' mental and physical health are essential to avoid abuse and serious complications.

Acknowledgments

Foundation to Support the Development of Teaching, Science, and Technology of the State of Mato Grosso do Sul (FUNDECT), National Council for Scientific and Technological Development (CNPq), Federal University of Grande Dourados.

Conflict of Interest

Authors must inform in this item whether or not there is a conflict of interest.

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