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Review Article

An Update on the Adverse Effects of Zolpidem Use

Uma atualização sobre os efeitos adversos do uso do zolpidem

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ABSTRACT

According to ANVISA, in recent years, there has been a significant increase in sales of Zolpidem, a notification that raises concern, as approximately 40% of the population experiences difficulty sleeping, insomnia disorder, using this as a justification for seeking the medication. However, the primary recommendation is to seek the root cause of the disorder. Zolpidem is a hypnotic-sedative drug, belonging to the imidazopyridine class, which acts in the treatment of insomnia, showing a good response in the induction and maintenance of sleep, but it presents various adverse effects. Therefore, a patient investigation should be conducted before choosing the treatment. The article aims to describe the adverse effects of prolonged use of Zolpidem and the possible health damages it may cause. This is a systematic literature review conducted in the digital databases of the Virtual Health Library (VHL), Google Scholar, PubMed, and Scielo. A total of 117 articles were found with the following descriptors: "Zolpidem," "adverse effects," and "anxiolytics." Inclusion criteria were review articles published in the last 16 years in English, Portuguese, and Spanish; exclusion criteria included restricted access articles, incomplete texts, and duplicates. The twelve selected studies point to insomnia, which can be primary or secondary, as a sleep disorder that, in addition to requiring an accurate diagnosis, needs a good evaluation for treatment decision, recommending limiting Zolpidem prescriptions to short-term treatment, as this drug presents various side effects, such as headache, falls, sleepwalking, amnesia, cognitive impairment, and it also poses risks to pregnant women and especially to the fetus, which may be born with low weight. In long-term treatment with Zolpidem, the drug may lose its effects, and the risk of dependence increases with the dose and duration. Throughout the development of the work, it was noted that Zolpidem had a significant increase in use, making it necessary to seek campaigns for the rational use of medications and pharmaceutical care during dispensing, so that the pharmacist can guide and clarify doubts about the use, risks of drug interactions, and the adverse effects that Zolpidem may present. It is noteworthy that there is little information about interactions, effects, and, mainly, campaigns for the rational use of medications. Therefore, more scientific studies on the topic are needed.

RESUMO

De acordo com a ANVISA, nos últimos anos, houve um aumento significativo nas vendas do Zolpidem, notificação que desperta preocupação, pois aproximadamente 40% da população

apresenta dificuldade para dormir, transtorno da insônia, sendo utilizada essa justificativa para a procura do consumo do medicamento. No entanto, a recomendação primária consiste na busca pela origem do que causa o transtorno. O Zolpidem é um fármaco de ação hipnótico-sedativo, pertencente à classe das imidazopiridinas, que atua no tratamento da insônia, apresentando uma boa resposta na indução e manutenção do sono, porém apresenta diversos efeitos adversos. Dessa forma, deve ser realizada uma investigação do paciente antes da escolha do tratamento. O artigo tem como objetivo descrever os efeitos adversos do uso prolongado do Zolpidem e os possíveis danos que trazem à saúde. Trata-se de uma revisão sistemática de literatura realizada nas bases de dados digitais da Biblioteca Virtual em Saúde (BVS), Google Acadêmico, PubMed e Scielo. Foram encontrados 117 artigos com os seguintes descritores "Zolpidem", "efeitos adversos" e "ansiolíticos". Como critérios de inclusão, estabeleceu-se artigos de revisão publicados nos últimos 16 anos nos idiomas em inglês, português e espanhol; como critérios de exclusão, definiu-se artigos de acesso restrito, textos incompletos e com duplicidade. Os doze estudos selecionados apontam a insônia, que pode apresentar caráter primário ou secundário, como um distúrbio do sono que, além de demandar um diagnóstico preciso, necessita de uma boa avaliação para decisão do tratamento, sendo recomendado limitar as prescrições de Zolpidem para tratamento a curto prazo, uma vez que esse fármaco apresenta diversos efeitos colaterais, como dor de cabeça, quedas, sonambulismo, amnésia, comprometimento cognitivo, além de possuir riscos às gestantes e, principalmente,ao feto, que pode nascer com baixo peso. Já no tratamento a longo prazo com o Zolpidem, o fármaco pode perder seus efeitos e o risco de dependência aumenta com a dose e a duração. Ao longo do desenvolvimento do trabalho, notou-se que o Zolpidem teve um aumento significativo na utilização, sendo necessário buscar por campanhas do uso racional de medicamentos e a atenção farmacêutica no ato da dispensação, a fim de que o profissional farmacêutico oriente e esclareça dúvidas sobre o uso, os riscos de interação medicamentosa e os efeitos adversos que o Zolpidem pode vir a apresentar. Destaca-se que há pouca informação sobre as interações, efeitos e, principalmente, campanhas do uso racional de medicamentos. Sendo assim, são necessários mais estudos científicos sobre o tema.

INTRODUCTION

Zolpidem is a non-benzodiazepine drug with sedative and hypnotic action, approved by the Food and Drug Administration (FDA) in 1992 in the United States (USA), widely prescribed for adult and elderly patients with insomnia[1]. Launched in the late 80s and known as Z-drugs, selective benzodiazepine receptor agonists[2], this medication is available in pharmaceutical forms such as tablets, extended-release tablets (ER), sublingual tablets, and oral spray[3], with 23 registered brands at the National Health Surveillance Agency (ANVISA).

Derived from imidazopyridines, the sedative effects caused by Zolpidem occur due to interaction with GABA A receptors with selective affinity for the α-1 subunit, triggering Central Nervous System (CNS) inhibition[4]. The drug is indicated for the treatment of occasional, transient, or chronic insomnia, acting in reducing sleep latency and increasing sleep duration (**figure 1**). Like all CNS depressant drugs, it presents various adverse effects such as drowsiness, headaches, dizziness, exacerbated insomnia, double vision, loss of balance, sleepwalking, and cognitive disorders (anterograde amnesia), which results in patient vulnerability, consequently increasing the risk of falls and fractures, especially in elderly patients[5,6]. According to ANVISA, between 2017 and 2020,

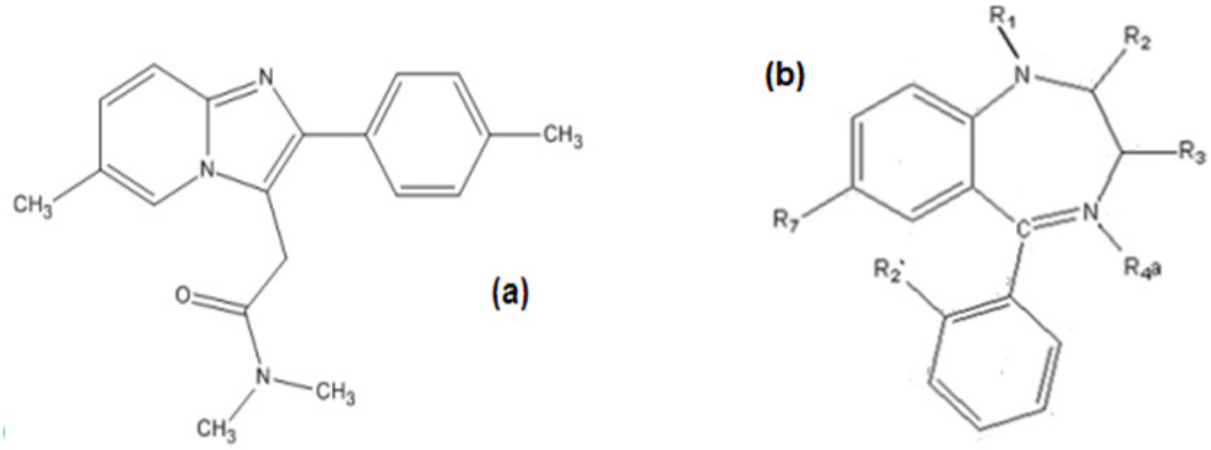

Figure 1 - Chemical structure of the Imidazopyridine class (Zolpidem) (a) and the Benzodiazepine class (b)

Zolpidem sales increased by 1215% in Brazil, with 234 million boxes sold, concerning data considering the risks of indiscriminate use of this drug.

According to the World Health Organization (WHO), approximately 40% of Brazilians report suffering from some sleep disorder, resulting in much tiredness and daytime sleepiness. Insomnia can be acquired idiopathically, psychophysiologically, or related to another acute or chronic clinical condition[56]. It is known that insomnia is a common disorder that increases with age, and to control this condition, non-pharmacological and pharmacological interventions are used. Thus, the most used medications for the treatment of insomnia can be from two different classes: imidazopyridines and benzodiazepines; this class differentiation is based on the site of action and chemical structure (**Figure 1**) of each drug class[5]. Before prescribing the drug, it is necessary to relate benefit and risk due to adverse effects, considering the age group and possible limitations to treatment[5].

The difficulty in sleeping, which is used as a justification for the use of sedative medications, reveals cultural, social, and family problems that need to be addressed in health services. When developing a pharmacological treatment, a broader investigation is needed, in addition to an understanding of the clinical condition and the conditions presented by the patient, so that a treatment can be prescribed that ensures the patient's quality of life, avoiding future and public health problems.

Given the significant increase in the use of this drug nowadays, it is necessary to understand the real problem presented by the patient, seeking safer alternatives so that the adverse effects considered uncommon do not cause harm to the patient. In this context, the objective of this work is to conduct a systematic literature review to analyze the adverse effects of prolonged use of Zolpidem and the possible health damages it may cause.

MATERIAL AND METHODS

The present study is a systematic literature review based on searches in the digital databases of the Virtual Health Library (BVS), Google Scholar, PubMed, and Scientific Electronic Library Online (Scielo). For the progress of this study, 117 articles were found using the following health science descriptors: “Zolpidem”, “adverse effects”, and “anxiolytics”. Filters were used: articles with full text and published in the last 20 years (2003 to 2023). In contrast, review articles in English, Portuguese, and Spanish were included and incomplete, restricted access, and duplicate texts were excluded.

Thirty articles were found after applying the descriptors and filters, and nineteen works

explaining the topic were selected. After reading the texts, twelve met the inclusion and exclusion criteria, addressing the aspects of the topic according to the objectives (**Table 1**). Figure 2 shows the process of searching and selecting the articles.

This manuscript was translated with the assistance of ChatGPT, an AI language model developed by OpenAI.

RESULTS AND DISCUSSION

Table 1 highlights the documents selected for the study in which the adverse effects of Zolpidem reported in the investigation were presented.

Insomnia is a disorder that affects all ages, characterized by difficulty initiating and maintaining sleep, resulting in daytime impairment. Zolpidem is an imidazopyridine hypnotic agent approved by the U.S. Food and Drug Administration (FDA) for the short-term treatment of insomnia in the United States (USA). Its popularity is likely the result of marketing due to initial reports of low daytime sedation and low abuse potential. However, post-marketing studies and case reports began to show that Zolpidem was associated with complex sleep-related behaviors such as driving, cooking, and talking while asleep[1].

A critical literature review conducted by Ribeiro et al. (2018)[12] showed that the use of medications acting on the CNS, such as anxiolytics, hypnotics, sedatives, antipsychotics, opioids, antiepileptics, and antidepressants, is susceptible to inducing fall incidents in patients.

In the late 1980s, non-benzodiazepine hypnotics emerged: Zolpidem, Zopiclone, Zaleplon, and Eszopiclone, known as Z-drugs or selective benzodiazepine receptor agonists[2]. The promise of Z-drugs was low rates of adverse effects, not leading to tolerance and dependence. However,

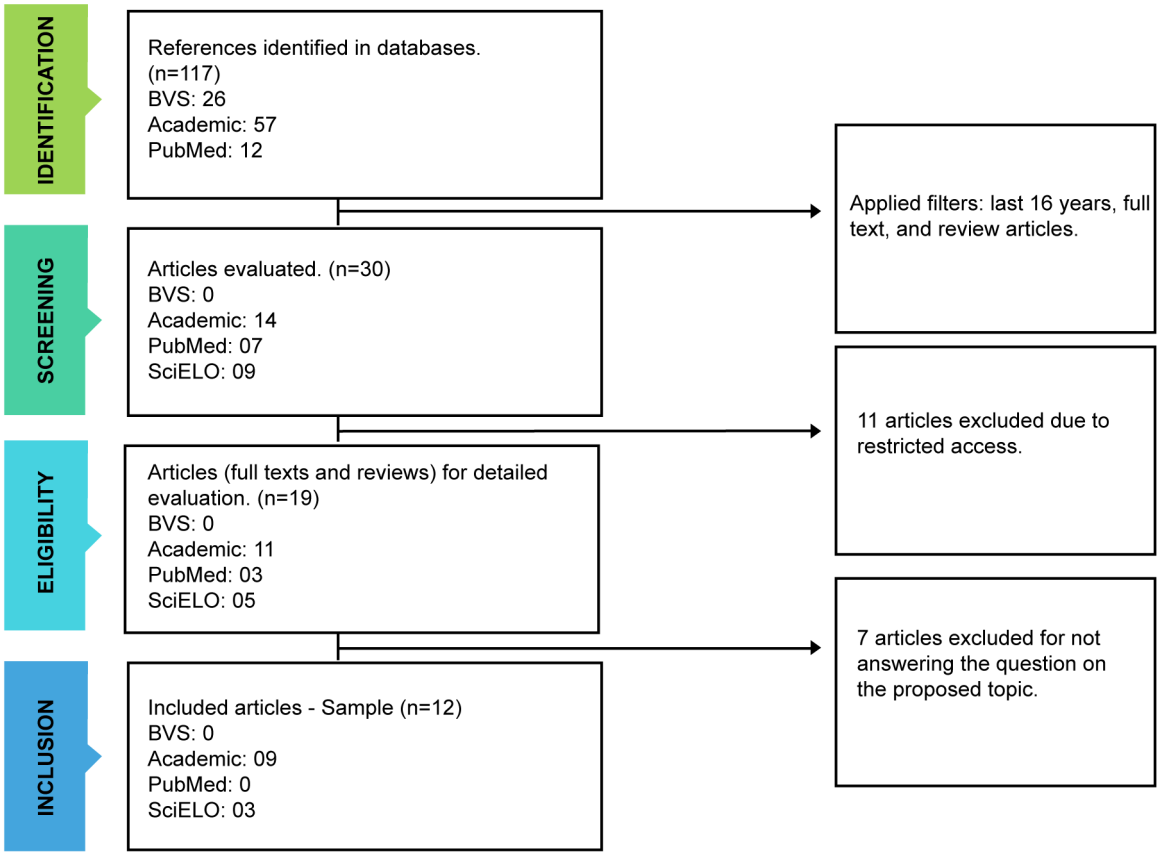

Figure 2 - Flowchart for the selection of documents on Zolpidem and adverse effects

Table 1. Articles on Zolpidem and Adverse Effects (2007-2023)

Author/Year	Objectives	Adverse Effects
ŚWIĄDER et al. 2023[7]	Current knowledge on evidence of harm caused by Z drugs and estimate the prevalence of dispensed prescriptions.	Cognitive impairment, memory impairment, confusion, dizziness, drowsiness, tolerance, dependence, and withdrawal.
ALAGIA et al. 2022[17]	Understand the long-term effects of continuous use of Zolpidem and seek safer alternatives for the treatment of insomnia in the elderly.	Falls.
ALVES; FERREIRA; SOUZA 2022[8]	Understand the benefits and consequences of Zolpidem use during the Covid-19 pandemic.	Cognitive impairment, car accident, and fractures.
SILVA; SOLIANI; SANCHES 2022[2]	Analyze the use and adverse reactions of Z-drugs.	Headache, drowsiness, and dizziness. There are risks of suicides and some reports of eating disorders.
AZEVEDO et al. 2022[5]	Analyze the pharmacotherapeutic profile of Zolpidem.	Headaches, drowsiness, dizziness, fatigue, diarrhea, vomiting, hallucinations, reality distortion, bone fractures, and sleepwalking.
FAGUNDES et al. 2022[9]	Possible risks and benefits and which drugs could be avoided, assisting the psychiatrist in the safe management of pharmacological treatment of insomnia during pregnancy.	In the fetus: low birth weight, premature birth, or cesarean section.
PAULA; JUSTINO, 2021[10]	Is Zolpidem safe?	Abuse and/or physical or psychological dependence, tolerance, exacerbation of insomnia, nightmares, nervousness, irritability, agitation, aggressiveness, rage, delusional ideas, hallucinations, inappropriate behavior, and other behavior disorders.
ROHDE, 2021[11]	Z drugs associated with transient global amnesia.	Transient global amnesia.
FERREIRA; SANTOS, 2021[6]	Investigate the outcomes of refractory patients discontinuing benzodiazepines and non-benzodiazepines who underwent therapy for insomnia and/or nighttime anxiety with the use of Cannabis sp. oil.	Ataxia, dizziness, hypersedation, amnesia, and dependence.
RIBEIRO et al. 2018[12]	Relationship between drugs and falls in hospitalized patients regardless of age.	Falls.
DALEY; McNIEL; BINDER, 2011[1]	Explore current understanding of specific psychopharmacology of Zolpidem.	Disinhibition, depersonalization, hallucinations, mood changes, anterograde amnesia, and sleepwalking.
WANNMACHER, 2007[4]	Risks and benefits of managing insomnia in the elderly.	Falls, confusion, delirium, withdrawal symptoms, and dependence.

Table 2. Pharmaceutical Forms of Zolpidem

Presentation	Dose (mg)
Zolpidem	5-10
Zolpidem LP	6,25-12,5
Zolpidem oral spray*	5-10
Zolpidem subligual	5

*not available in Brazil

Z-drugs in long-term treatment may lose their effects, and the risk of dependence or abuse increases with dose and duration of treatment.

Before prescribing a Z-drug hypnotic, the physician should identify if it is the ideal treatment for the patient, considering whether the patient lives alone, uses other controlled medications, or uses other drugs concurrently, as these factors are considered risks for transient global amnesia. When choosing Z-drugs as a treatment option, it is necessary to inform the patient about a possible effect of transient global amnesia so that it can be recognized early and reported[11].

Although Zolpidem presents various adverse effects, its use can bring significant relief for some patients. Therefore, Zolpidem should be employed only in the short term, not exceeding four weeks, being used for 2 to 5 days for occasional insomnia cases and 2 to 3 weeks for transient insomnia cases. Additionally, Zolpidem should be administered in low doses for the elderly over 65 years, due to their higher sensitivity to adverse effects, and for women, as studies have shown that women take longer to eliminate the drug from the body, leading to 45% higher blood concentrations[10].

Sleep disorders are prevalent during pregnancy[9]. These sleep alterations during pregnancy constitute a complex and current maternal health problem affecting all age groups, severely impacting the quality of life of pregnant women. Among the drugs most used in studies are benzodiazepines, hypnotics, sedatives, antidepressants, antihistamines, and antipsychotics, with sedative-hypnotics such as benzodiazepines and non-benzodiazepine hypnotics being the most used. The use of Zolpidem during pregnancy, when used for a short period, can improve insomnia, although its use may result in low birth weight, cesarean delivery, and preterm birth. It is important to emphasize that all medications used to treat insomnia during pregnancy should be administered with caution, in low doses, and for a limited period.

According to the FDA, since 1979, a letter classification system has been used to organize medications into five categories (A, B, C, D, and X)[16].

Adverse reactions can be considered very common (≥ 10%), common (≥ 1 and < 10%), uncommon (≥ 0.1 and < 1%), rare (≥ 0.01 and < 0.1%), or very rare (< 0.01%)[5]. Hallucinations have been reported after 30 minutes of taking the medication. These hallucinations may occur more frequently when used concurrently with antidepressant medications. This happens due to the characteristic of antidepressants to inhibit the enzyme CYP3A4, responsible for metabolizing Zolpidem. At this stage, metabolism is inhibited, the drug remains in the bloodstream, and the occurrence of hallucinations increases.

The drug leaflet from EMS/SA on ANVISA states that according to the recommendations of the Council for International Organizations of Medical Sciences (CIOMS), the following frequen-

cy indices have been used: Very Common: ≥ 10%; Common: ≥ 1 and < 10%; Uncommon: ≥ 0.1 and < 1%; Rare: ≥ 0.01 and < 0.1%; Very Rare: < 0.01%; and Isolated Cases: cannot be estimated with available data (**Table 4**).

Prolonged use for several weeks can cause tolerance, i.e., decreased efficacy of the drug, in addition to a high risk of psychological and physical dependence, which increases with dose and duration of treatment[7]. Abrupt discontinuation can cause withdrawal symptoms, including headaches, muscle pain, anxiety, agitation, irritability, and seizures. Abrupt drug discontinuation can also lead to rebound syndrome, i.e., the return of symptoms for which the drug was prescribed. To avoid these symptoms, gradual dose reduction is recommended.

In the elderly, there is an increased consumption of Zolpidem with age. Its continuous use is accompanied by potential risks, especially falls. The elderly are more sensitive to CNS depressants, accentuating the effects for a given plasma

Table 4. Adverse reactions found in the Zolpidem Hemitartrate leaflet

Types of Disorders	Common	Uncommon	Isolated Cases
CNS Disorders	Drowsiness, headache, dizziness, exacerbated insomnia, anterograde amnesia (amnesia effects may be associated with inappropriate behavior).	-	Depressed level of consciousness.
Psychiatric Disorders	Hallucinations, agitation, nightmares.	Confusion, irritability.	Nervousness, aggressiveness, delusion, rage, inappropriate behavior, sleepwalking (see "Use in the Elderly, Children, and Other Risk Groups"), dependence (withdrawal syndrome or rebound effect may occur after treatment discontinuation), libido alteration. Most psychiatric disorders are related to paradoxical reactions.
General Disorders	Fatigue.	-	Gait disturbances, drug resistance, fall (especially in elderly patients and when Zolpidem is not administered according to recommendations).
Ocular Disorders	-	Diplopia	-
Gastrointestinal Disorders	Diarrhea, nausea, vomiting, abdominal pain.	-	-
Musculoskeletal and Connective Tissue Disorders	-	-	Muscle weakness.
Skin and Subcutaneous Tissue Disorders	-	-	Rash, pruritus, urticaria, hyperhidrosis.
Hepatobiliary Disorders	-	-	Increased liver enzymes.
Immune System Disorders	-	-	Angioedema.

concentration. Cognitive impairments, confusion, delirium, withdrawal symptoms, and dependence may arise. Therefore, caution is recommended for use in this age group[4].

According to Alagia et al. (2022)[17], Zolpidem is indicated for the treatment of insomnia and, when compared to other drugs, has low contraindication. However, even being one of the best options for treating insomnia, Zolpidem still causes effects that can be harmful, especially in the elderly population, such as an increased risk of falls, as one of its effects is causing postural instability. Therefore, attention is necessary for the greater sustainability of the elderly to the appearance of the consequences of using this medication, especially the increased potential risk of falls due to the reduction of clearance rates and the increase in peak serum levels, the concentration of these drugs. Fractures and injuries caused by falls impair functional capacity, health, and consequently the quality of life in the long term. These prescriptions should be limited to reduce the risk of patient imbalance.

Drug Interactions (DI) are clinical events that can occur when there is interference from a secondary drug, food, or drug, which can increase or decrease the expected effect. Zolpidem can have moderate interactions with numerous drugs, and with drugs associated with Paracetamol with Hydrocodone, severe interactions can occur. When Zolpidem is administered with other drugs such as diphenhydramine, Duloxetine, Escitalopram, Pregabalin, Metoprolol, Alprazolam, and Cetirizine, the side effects resulting from drug interactions are very similar, causing drowsiness, confusion, difficulty concentrating, and dizziness. Metoprolol Succinate is a selective beta-1 blocker drug indicated for the treatment of arterial hypertension, and when administered concurrently with Zolpidem, additive effects on blood pressure reduction can occur, causing side effects such as headache, dizziness, vertigo, fainting, and/or changes in heart rate. The drug combination of Paracetamol with Hydrocodone, a narcotic analgesic drug widely used for the treatment of acute pain crises, when administered with drugs that also cause CNS depression, as is the case with Zolpidem, can lead to severe interactions and side effects, including respiratory discomfort, coma, and even death[5].

Figure 3 shows a relationship of adverse effects of Zolpidem, highlighting those that presented the most reports among the studied articles. Among them, the adverse effect of fall/fracture stands out, where there was a greater prevalence due to the higher use of Zolpidem in elderly patients.

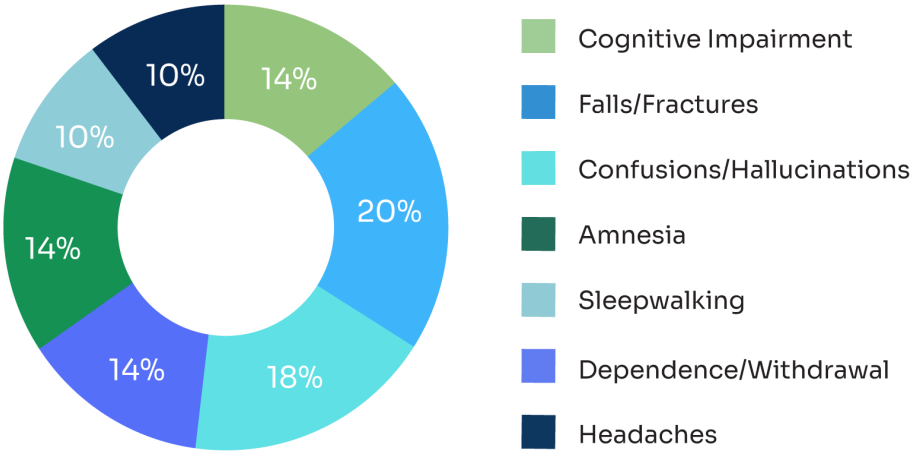

Figure 3 – Percentage of adverse effects concerning those found in documents about Zolpidem

Pharmaceutical care is the most crucial task of the pharmacist, involving direct interaction, guidance, and supervision of patients who frequently arrive without information. The pharmacist is the main link between the prescriber and the patient, providing essential information colloquially to avoid adverse events, drug interactions, and waste, thus reducing the potential risks of abuse and drug dependence[5].

The rational use of drugs is an important topic to be highlighted, discussed, and raised awareness among the population worldwide due to high self-medication rates, interruption, and/or drug changes without the prescription of a doctor or other qualified health professional, such as the pharmacist. When used irrationally, the imidazopyridine class can bring consequences to the patient regarding physical and psychological states. Therefore, pharmaceutical care in the act of dispensing Zolpidem is extremely important, where during the product dispensation, the pharmacist should guide the patient on the adverse effects the patient may present and the importance of treatment duration to prevent future problems and public health issues[5, 10].

Marketed in the form of Zolpidem Hemitartrate, this drug is indicated for the treatment of insomnia. Patients affected by this disorder opt for Zolpidem treatment due to the drug being less associated with dependence and generating fewer adverse effects compared to benzodiazepines. Given the advantages presented in pharmacological treatment with Zolpidem for insomnia, it was observed that in recent years there was a significant increase in the commercialization and consumption of the drug, generating various reports of adverse effects not recorded in the leaflet.

Zolpidem presents numerous adverse effects considered very common (such as headaches, dizziness, drowsiness) and uncommon (such as cognitive impairment, memory impairment, hallucinations, sleepwalking, amnesia, fractures, and falls, dependence, agitation, nightmares, confusion, irritability, nervousness, aggressiveness, and in rare cases, eating disorder, delusion, rage, inappropriate behavior, libido alteration, gait disturbances, drug resistance, and in pregnant women, the reported adverse effects can cause low birth weight in the fetus and possible preterm or cesarean delivery). Zolpidem should be used with the indication of a health professional with caution and for a limited time according to the risk classification in pregnant women.

The use of Zolpidem is indicated for short-term insomnia treatment, as when used long-term, it presents risks of losing its efficacy and the appearance of adverse effects, causing health damage, especially in the elderly, such as car accidents and bone fractures. Therefore, pharmaceutical care in dispensing Zolpidem is extremely important, offering understandable guidance to the patient, considering their conditions, to control and prevent harmful effects from proper use, promoting the campaign for the rational use of this drug class.

Given this, it is necessary to develop more scientific studies on the topic to ensure that users of this drug can understand the possible adverse effects, as there is little information and references on the discussed topic.

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