Integrative Review of Zolpidem and Insomnia: Efficacy, Safety, and Adverse Effects

Revisão Integrativa sobre Zolpidem e Insônia: Eficácia, Segurança e Efeitos Adversos

Revisión Integrativa sobre Zolpidem e Insomnio: Eficacia, Seguridad y Efectos Adversos

Gabriella Menezes Camargo[1], Clarissa de Deus Lemos[2], Ana Luiza Souza Nunes[3], Brenno Eike Gomes Junqueira[4], Bruna Wu Zhao[5], Maria Eduarda Maciel de Oliveira[6], Pedro Gabriel Trancoso Cortez[7]

Como citar: Camargo GM, Lemos CD, Nunes ALS, Junqueira BEG, Zhao BW, Oliveira MEM, Cortez PGT. Integrative Review of Zolpidem and Insomnia: Efficacy, Safety, and Adverse Effects. REVISA. 2026; 15(Esp.4): 20-6. Doi: https://doi.org/10.36239/revisa.v15.nEsp4.p20a26

REVISA

1. Universidade de Rio Verde, Formosa, Goiás, Brasil. https://orcid.org/0009-0001-9674-0307

2. Universidade de Rio Verde, Formosa, Goiás, Brasil https://orcid.org/0009-0008-6626-2341

3. Universidade de Rio Verde, Formosa, Goiás, Brasil. https://orcid.org/0009-0001-9674-0307

4. Universidade de Rio Verde, Formosa, Goiás, Brasil. https://orcid.org/0009-0004-7606-2619

5. Universidade de Rio Verde, Formosa, Goiás, Brasil. https://orcid.org/0000-0002-0147-2064

6. Universidade de Rio Verde, Formosa, Goiás, Brasil. https://orcid.org/0000-0001-8220-8507

7. Universidade de Rio Verde, Formosa, Goiás, Brasil. https://orcid.org/0009-0000-9876-3142

8. Escola Superior de Ciências da Saúde, Distrito Federal, Brasília, Brasil https://orcid.org/0009-0004-4518-1594

Recebido 27/01/2026
Aprovado: 22/03/2026

RESUMO

Objetivo: O Zolpidem, um hipnótico não benzodiazepínico de ação rápida, amplamente utilizado no manejo da insônia, tem sido alvo de crescente investigação quanto à sua eficácia, perfil de efeitos adversos e segurança. Esta revisão integrativa, realizada nas bases BVS, SciELO e Cochrane, identificou inicialmente 2.354 artigos, dos quais 7 preencheram os critérios de inclusão, publicados entre 2019 e 2024. As evidências indicam que o zolpidem reduz a latência do sono e melhora a percepção de qualidade do sono, com maior eficácia em doses baixas, formulações de liberação imediata e uso de curto prazo. Contudo, o fármaco associa-se a eventos adversos sendo os principais sonolência residual, alterações cognitivas, distúrbios de memória e comportamentos complexos do sono, com maior prevalência em mulheres e idosos. Conclui-se que o zolpidem é uma ferramenta terapêutica relevante no tratamento da insônia, mas seu uso deve ser pautado por prescrição criteriosa, monitoramento contínuo e preferência por estratégias não farmacológicas sempre que possível, especialmente em populações vulneráveis.

Palavras-chave: Zolpidem; Medicamentos Indutores do Sono; segurança; Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos; Uso Indevido de Medicamentos.

ABSTRACT

Objective: Zolpidem, a fast-acting non-benzodiazepine hypnotic, is widely used in the management of insomnia and has been the focus of increasing investigation regarding its efficacy, adverse effect profile, and safety. This integrative review, conducted in the BVS, SciELO, and Cochrane databases, initially identified 2,354 articles, of which 7 met the inclusion criteria, published between 2019 and 2024. Evidence indicates that zolpidem reduces sleep latency and improves perceived sleep quality, with greater efficacy at low doses, immediate-release formulations, and short-term use. However, the drug is associated with adverse events, mainly residual drowsiness, cognitive changes, memory disturbances, and complex sleep behaviors, with higher prevalence in women and older adults. It is concluded that zolpidem remains a relevant therapeutic tool for the treatment of insomnia, but its use should be guided by strict prescribing criteria, continuous monitoring, and preference for non-pharmacological strategies whenever possible, especially in vulnerable populations.

Keywords: Zolpidem; Sleep Aids; Safety; Drug-Related Side Effects and Adverse Reactions; Prescription Drug Misuse.

RESUMEN

Objetivo: El zolpidem, un hipnótico no benzodiacepínico de acción rápida, es ampliamente utilizado en el manejo del insomnio y ha sido objeto de creciente investigación en cuanto a su eficacia, perfil de efectos adversos y seguridad. Esta revisión integrativa, realizada en las bases BVS, SciELO y Cochrane, identificó inicialmente 2.354 artículos, de los cuales 7 cumplieron los criterios de inclusión, publicados entre 2019 y 2024. La evidencia indica que el zolpidem reduce la latencia del sueño y mejora la percepción de la calidad del mismo, con mayor eficacia en dosis bajas, formulaciones de liberación inmediata y uso a corto plazo. Sin embargo, el fármaco se asocia a eventos adversos, principalmente somnolencia residual, alteraciones cognitivas, trastornos de memoria y comportamientos complejos del sueño, con mayor prevalencia en mujeres y ancianos. Se concluye que el zolpidem sigue siendo una herramienta terapéutica relevante para el tratamiento del insomnio, pero su uso debe basarse en criterios estrictos de prescripción, monitoreo continuo y preferencia por estrategias no farmacológicas siempre que sea posible, especialmente en poblaciones vulnerables.

Descriptores: Zolpidem; Inductores del Sueño; Seguridad; Efectos Adversos Relacionados con Medicamentos; Uso Indebido de Medicamentos.

Introduction

Zolpidem is a fast-acting non-benzodiazepine hypnotic agent belonging to the imidazopyridine class, widely used in the treatment of sleep disorders, particularly insomnia. Initially available in immediate-release (IR) and extended-release (ER) formulations, it now also comes in sublingual tablets in standard (SD) and low-dose (LD) forms, as well as oral spray, allowing for faster absorption by bypassing the gastrointestinal tract.[1] Its efficacy ranges from transient to chronic insomnia, both primary and comorbid types, and covers various populations.[1,2]

Although generally considered safe, Zolpidem can cause neuropsychiatric effects such as hallucinations, amnesia, and sensory distortions, especially in women and at doses above 10 mg. These adverse events, frequently reported in the literature, occur between 20 and 30 minutes after ingestion and tend to resolve spontaneously within a few hours.[2] Other common effects include headache, drowsiness, and dizziness, with a low incidence of confusion (<1%).[1,2] Research indicates that individual differences in CYP3A4 metabolism, gender, dosage, and drug interactions influence the occurrence of such events. Notably, women exhibit serum concentrations about 40% higher, which may explain the greater prevalence of adverse reactions in this population.[2]

This integrative review aims to analyze the safety, efficacy, tolerance, and impacts of zolpidem use, highlighting the main clinical studies and reviews. The objective is to deepen the understanding of the drug's risks and benefits, supporting safer clinical decision-making.

Objectives

To investigate the safety of prolonged zolpidem use in sleep disorders, assessing its impact on quality of life, including dependence and tolerance, and characterizing the main neurological, cognitive, and behavioral adverse effects.

Methodology

The methodology of this research consists of an integrative literature review on the efficacy, side effects, and safety of Zolpidem, conducted in seven stages: definition of the research question; inclusion and exclusion criteria; data selection and extraction; analysis and interpretation; and presentation of the review with a flowchart and results table. The guiding question was developed using the PICo acronym, referring to Population (P), Intervention (I), and Context (Co), as detailed below: P = Zolpidem; I = clinical implications; Co = safe use.

Searches were conducted in the electronic databases of the Virtual Health Library of the Ministry of Health (BVS), Scientific Electronic Library Online (SciELO), and Cochrane Database of Systematic Reviews (CDSR). Controlled terms from the Health Sciences Descriptors (DeCS) and the Boolean operators "AND" and "OR" were used. The

keywords were: "Zolpidem"; "Sleep Aids"; "Safety"; "Drug-Related Side Effects and Adverse Reactions"; "Prescription Drug Misuse."

Searches were performed independently by three researchers, with disagreements resolved by consensus.

During bibliographic selection, 2,354 articles were screened; 1,537 were excluded for being over five years old, 14 for incomplete access, 127 for being guides, books, or manuals, and 364 after title review. Of the 255 full-text studies (2019–2024), 70 duplicates were removed, totaling 185. After title screening, 147 were evaluated, followed by abstract reading, resulting in 50 articles, 13 of which answered the guiding question (Figure 1).

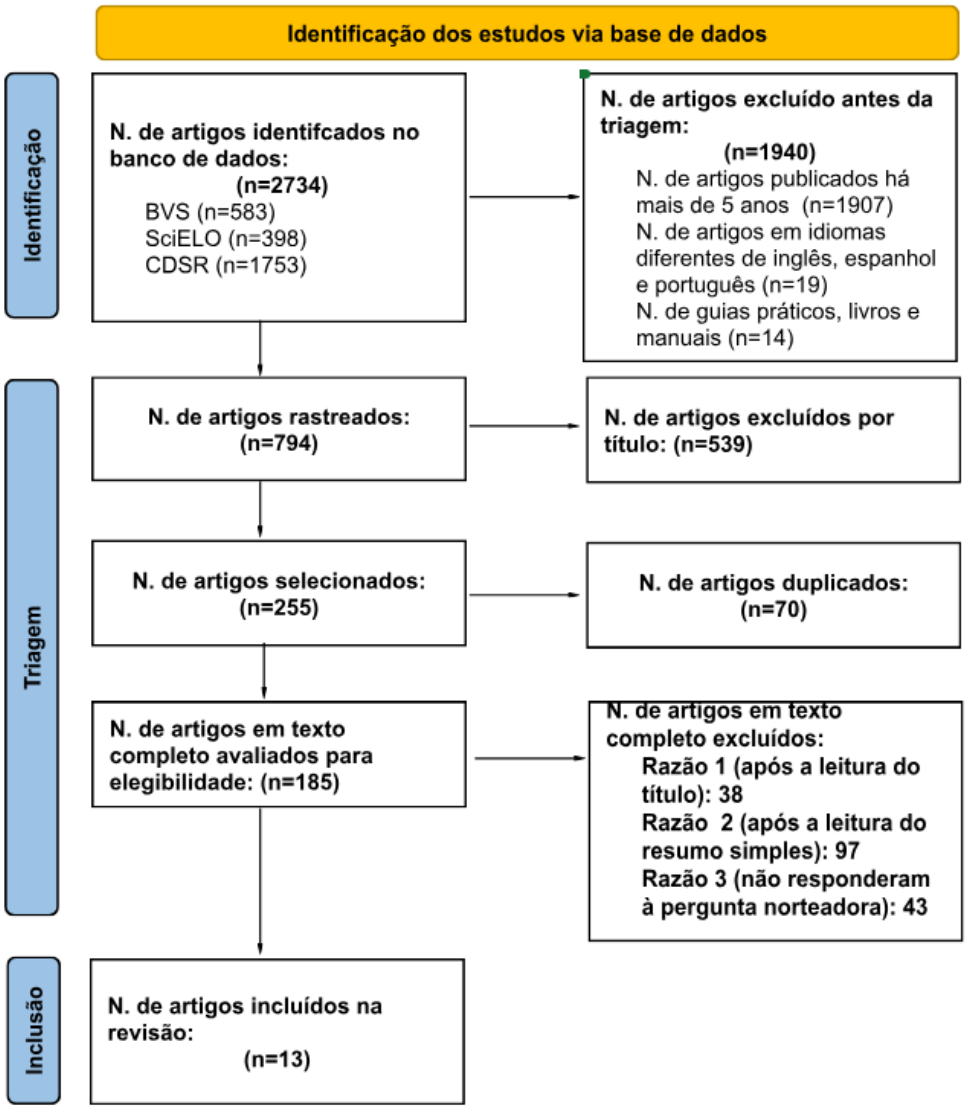

Figure 1– Flowchart of bibliographic research. Source: prepared by the authors following PRISMA guidelines.

Discussion and Results

Zolpidem is a GABAergic agonist widely used as a sleep inducer, with a half-life of approximately 1.5 to 3.2 hours and a peak plasma concentration reached about 1.6 hours after ingestion.[3] Despite its hypnotic effect, which enhances neuronal inhibitory tone, zolpidem does not act uniformly across all sleep stages, potentially suppressing REM sleep and slightly increasing stage N3.[1,4]

In terms of adverse effects, the drug may impair cognitive performance, reduce processing speed and perceptual learning, and cause dizziness, fatigue, nausea, and excessive sleepiness.[3],[5] Zolpidem may improve episodic memory without affecting motor learning, but extended-release formulations (6–8 h) can impair memory depending on dose and formulation.[3] Lower doses show better safety, with an initial 6.25 mg dose recommended for patients ≥65 years and all women to reduce adverse effects.[4]

From a neuromotor perspective, zolpidem is effective in treating task-specific focal dystonias, common in writers and musicians.[6] It may be useful in alcohol withdrawal, although its effects differ from ethanol, acting on the α1 subunit of GABA receptors and potentially causing either sedation or stimulation. Additionally, it may potentiate ethanol-induced behavioral sensitization via α1GABA_A receptors in the VTA and mesolimbic dopaminergic neuroadaptations, possibly promoting compulsive behaviors and reinforcing the need for strict monitoring.[7]

Although initially considered a safer alternative to benzodiazepines, zolpidem poses significant risks, including hallucinations, delirium, amnesia, and complex sleep behaviors (CSBs) such as sleepwalking, driving, and eating while asleep. These events occur in up to 4.7% of cases, more frequently in women, doses above 10 mg/day, and when patients fail to go to bed immediately after administration. In response, the FDA issued warnings in 2007, 2013, and 2019, including a black box warning about serious injuries and deaths, emphasizing the need for careful prescription and clinical monitoring.[8]

In elderly patients, acute zolpidem use is not associated with significant cognitive impairment but may cause balance dysfunction even at usual doses (5–10 mg), increasing the risk of falls, fractures, and injuries, particularly in those with pre-existing conditions. Careful prescribing, mobility monitoring, and preventive measures such as exercise are recommended to improve sleep without compromising safety.[9,10]

In hemodialysis patients, zolpidem use increased the risk of hospitalized fractures within 30 days, especially at high doses. About one-third received doses above those recommended for older adults, women, and frail patients, revealing clinical gaps. Elderly, frail, or CNS polypharmacy users showed higher risk, with no significant sex differences. In comparison, trazodone showed a more favorable safety profile, highlighting the importance of careful therapeutic decisions and non-pharmacological strategies such as cognitive-behavioral therapy.[11]

Lemborexant demonstrated superior efficacy to placebo and an advantage over zolpidem in sleep onset among individuals ≥55 years, reducing latency and increasing total rest time with sustained effects. The reduction in wake time occurred mainly in the latter half of sleep, indicating benefits in sleep-maintenance insomnia. The drug was well tolerated, with adverse events and discontinuation rates comparable to placebo, showing a favorable profile compared to traditional hypnotics.[12]

Currently, zolpidem has also been used as an adjuvant in postoperative functional recovery, especially in orthopedic procedures, relieving pain, anxiety, and inflammatory response. Trials indicate that the 5 mg tartrate formulation shows a lower incidence of perioperative adverse effects such as rebound insomnia, hangover, and mild anxiety.[13]

Therefore, zolpidem demonstrates efficacy as a sleep inducer, but its adverse effects, especially in vulnerable populations such as the elderly and hemodialysis patients, reinforce the need for individualized prescription, rigorous monitoring, and prioritization of non-pharmacological strategies whenever possible.

Final Considerations

This study confirms that zolpidem is an effective tool in the treatment of insomnia, improving sleep and daytime functionality, particularly in postoperative functional recovery. However, its use must follow strict criteria due to the risk of adverse events, dependence, and misuse. Thus, the need for clear protocols, patient education, monitoring, and further studies on long-term safe alternatives is emphasized.

References

1. Monti JM, Spence DW, Buttoo K, Pandi-Perumal SR. Zolpidem's use for insomnia. Asian J Psychiatr [Internet]. 2017 Feb [cited 2025 Sep 8];25:79-90. Available from: https://doi.org/10.1016/j.ajp.2016.10.006

2. Inagaki T, Miyaoka T, Tsuji S, Inami Y, Nishida A, Horiguchi J. Adverse reactions to zolpidem: case reports and a review of the literature. Prim Care Companion J Clin Psychiatry [Internet]. 2010 [cited 2025 Sep 8];12(6):PCC.09r00849. Available from: https://doi.org/10.4088/PCC.09r00849bro

3. Zhang J, Yetton B, Whitehurst LN, Naji M, Mednick SC. The effect of zolpidem on memory consolidation over a night of sleep. Sleep [Internet]. 2020 Nov [cited 2025 Sep 8];43(11):zsaa084. Available from: https://doi.org/10.1093/sleep/zsaa084

4. Moline M, Zammit G, Cheng J, Perdomo C, Kumar D, Mayleben D. Comparison of the effect of lemborexant with placebo and zolpidem tartrate extended release on sleep architecture in older adults with insomnia disorder. J Clin Sleep Med [Internet]. 2021 Jun [cited 2025 Sep 8];17(6):1167-74. Available from: https://doi.org/10.5664/jcsm.9180

5. Neylan TC, Richards A, Metzler TJ, Ruoff LM, Varbel J, O'Donovan A, et al. Acute cognitive effects of the hypocretin receptor antagonist almorexant relative to zolpidem and placebo: a randomized clinical trial. Sleep [Internet]. 2020 Oct [cited 2025 Sep 8];43(10):zsaa080. Available from: https://doi.org/10.1093/sleep/zsaa080

6. Vogelnik Žakelj K, Trošt M, Tomše P, Petrović IN, Tomić Pešić A, Radovanović S, Kojović M. Zolpidem improves task-specific dystonia: a randomized clinical trial integrating exploratory transcranial magnetic stimulation and [18F]FDG-PET imaging. Parkinsonism Relat Disord [Internet]. 2024 [cited 2025 Sep 8];124:107014. Available from: https://doi.org/10.1016/j.parkreldis.2024.107014

7. Brandão NRN, Libarino-Santos M, Marinho EAV, Oliveira TS, Borges ALN, Oliveira AP, et al. Treatment with zolpidem after ethanol administration potentiates the expression of ethanol-induced behavioral sensitization in mice. Braz J Med Biol Res [Internet]. 2020 [cited 2025 Sep 8];53(8):e10034. Available from: https://doi.org/10.1590/1414-431X202010034

8. Mittal N, Mittal R, Gupta MC. Zolpidem for insomnia: a double-edged sword. A systematic literature review on zolpidem-induced complex sleep behaviors. Indian J Psychol Med [Internet]. 2021 Sep [cited 2025 Sep 8];43(5):373-81. Available from: https://doi.org/10.1177/0253717621992372

9. Tavares G, Kelmann G, Tustumi F, Tundisi CN, Silveira BRB, Barbosa BMAC, et al. Cognitive and balance dysfunctions due to the use of zolpidem in the elderly: a systematic review. Dement Neuropsychol [Internet]. 2021 Sep [cited 2025 Sep 8];15(3):396-404. Available from: https://doi.org/10.1590/1980-57642021dn15-030013

10. Uemura SI, Imanishi A, Terui Y, Park I, Satake M, Han G. Residual effects of low dose of suvorexant, zolpidem, and ramelteon in healthy elderly subjects: a randomized double-blind study. Neuropsychopharmacol Rep [Internet]. 2022 Jun [cited 2025 Sep 8];42(2):288-98. Available from: https://doi.org/10.1002/npr2.12262

11. Assimon MM, Flythe JE. Zolpidem versus trazodone initiation and the risk of fall-related fractures among individuals receiving maintenance hemodialysis. Clin J Am Soc Nephrol [Internet]. 2020 Dec [cited 2025 Sep 8];16(1):88-97. Available from: https://doi.org/10.2215/CJN.10070620

12. Rosenberg R, Murphy P, Zammit G, Mayleben D, Kumar D, Dhadda S, et al. Comparison of lemborexant with placebo and zolpidem tartrate extended release for the treatment of older adults with insomnia disorder: a phase 3 randomized clinical trial. JAMA Netw Open [Internet]. 2019 Dec 2 [cited 2025 Sep 8];2(12):e1918254. Available from: https://doi.org/10.1001/jamanetworkopen.2019.18254

13. Jing W, Chunlin Z, Xue Y, Tingting H, Linyan Y, Xiao C, Lingli L. A randomized controlled study of a psycho-behavioral intervention combined with a non-benzodiazepine to improve perioperative sleep quality in patients undergoing knee arthroplasty. Front Surg [Internet]. 2023 [cited 2025 Sep 8];10:1113577. Available from: https://doi.org/10.3389/fsurg.2023.1113577

Correspondent author:
Gabriella Menezes Camargo
Via 13, nº 240, Ap. G02, Condomínio Park Prime 2,
Setor Sul, CEP: 73802-419.
Formosa, Goiás, Brasil.
gabriella.artigos@gmail.com