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# CURRENT EVIDENCE ON THE USE OF MELATONIN FOR PRIMARY INSOMNIA COMPARED TO BENZODIAZEPINES

# EVIDÊNCIAS ATUAIS SOBRE O USO DA MELATONINA NA INSÔNIA PRIMÁRIA EM COMPARAÇÃO AOS BENZODIAZEPÍNICOS

# EVIDENCIA ACTUAL SOBRE EL USO DE MELATONINA EN EL INSOMNIO PRIMARIO EN COMPARACIÓN CON LAS BENZODIAZEPINAS

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## ABSTRACT

Primary insomnia is one of the most prevalent sleep disorders in the adult population, characterized by difficulty in initiating or maintaining sleep, resulting in significant impairments to health, cognitive performance, and quality of life. Benzodiazepines and GABA-A receptor agonists, known as Z-drugs, are widely used in the pharmacological treatment of insomnia; however, their long-term use is associated with tolerance, dependence, and cognitive

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impairment. Melatonin, an endogenous hormone responsible for regulating the sleep–wake cycle, has been studied as a safe and physiological therapeutic alternative. This study aimed to analyze the most recent scientific evidence on the efficacy and safety of melatonin and its melatonergic agonists compared to benzodiazepines in the treatment of primary insomnia. An integrative literature review was conducted based on studies published between 2015 and 2025 in PubMed, SciELO, ScienceDirect, and Scopus databases. The results demonstrated that melatonin shows moderate efficacy in sleep onset and maintenance, with a superior safety profile and absence of dependence potential, making it a suitable therapeutic option, especially for elderly and polymedicated patients. It is concluded that melatonin represents a promising, effective, and safe pharmacological alternative for the management of primary insomnia, contributing to more rational clinical practices aligned with evidence-based medicine.

**Keywords:** Melatonin. Primary Insomnia. Benzodiazepines. Sleep Therapy. Clinical Pharmacology.

**RESUMO**

A insônia primária é um dos distúrbios do sono mais prevalentes na população adulta, caracterizando-se pela dificuldade em iniciar ou manter o sono, resultando em prejuízos significativos para a saúde, o desempenho cognitivo e a qualidade de vida. Os benzodiazepínicos e os agonistas dos receptores GABA-A, conhecidos como Z-drugs, são amplamente utilizados no tratamento farmacológico da insônia, porém seu uso prolongado está associado a tolerância, dependência e comprometimento cognitivo. A melatonina, hormônio endógeno responsável pela regulação do ciclo sono-vigília, tem sido estudada como alternativa terapêutica segura e fisiológica. Este estudo teve como objetivo analisar as evidências científicas mais recentes sobre a eficácia e a segurança da melatonina e de seus agonistas melatoninérgicos em comparação aos benzodiazepínicos no tratamento da insônia primária. Trata-se de uma revisão integrativa de literatura, baseada em artigos publicados entre 2015 e 2025 nas bases PubMed, SciELO, ScienceDirect e Scopus. Os resultados demonstraram que a melatonina apresenta eficácia moderada na indução e manutenção do sono, com perfil de segurança superior e ausência de potencial de dependência, configurando-se como alternativa terapêutica adequada, especialmente para idosos e pacientes polimedicados. Conclui-se que a melatonina representa uma opção farmacológica promissora, eficaz e segura para o manejo da insônia primária, contribuindo para práticas clínicas mais racionais e alinhadas à medicina baseada em evidências.

**Palavras-chave:** Melatonina. Insônia Primária. Benzodiazepínicos. Terapia do Sono. Farmacologia Clínica.

**RESUMEN**

El insomnio primario es uno de los trastornos del sueño más prevalentes en la población adulta, caracterizado por dificultad para iniciar o mantener el sueño, resultando en deterioros significativos para la salud, el rendimiento cognitivo y la calidad de vida. Las benzodiazepinas y los agonistas del receptor GABA-A, conocidos como fármacos Z, son ampliamente utilizados en el tratamiento farmacológico del insomnio; sin embargo, su uso prolongado se asocia con tolerancia, dependencia y deterioro cognitivo. La melatonina, una hormona endógena responsable de regular el ciclo sueño-vigilia, ha sido estudiada como una alternativa terapéutica segura y fisiológica. Este estudio tuvo como objetivo analizar la evidencia científica más reciente sobre la eficacia y seguridad de la melatonina y sus

agonistas de melatonina en comparación con las benzodiazepinas en el tratamiento del insomnio primario. Esta es una revisión bibliográfica integradora, basada en artículos publicados entre 2015 y 2025 en las bases de datos PubMed, SciELO, ScienceDirect y Scopus. Los resultados demostraron que la melatonina tiene una eficacia moderada para inducir y mantener el sueño, con un perfil de seguridad superior y sin potencial de dependencia, lo que la convierte en una alternativa terapéutica adecuada, especialmente para pacientes mayores y polimedicados. Se concluye que la melatonina representa una opción farmacológica prometedora, eficaz y segura para el tratamiento del insomnio primario, contribuyendo a prácticas clínicas más racionales y alineadas con la medicina basada en la evidencia.

**Palabras clave:** Melatonina. Insomnio Primario. Benzodiazepinas. Terapia del Sueño. Farmacología Clínica.

## 1 INTRODUCTION

Primary insomnia is one of the most prevalent sleep disorders in the adult population, characterized by difficulty in initiating or maintaining sleep, with a significant impact on quality of life, mood, cognitive performance, and daytime functioning. It is estimated that approximately 10 to 15% of the adult population suffers from chronic insomnia, with this prevalence being higher among women and the elderly (Riemann et al., 2017). The condition is associated with relevant clinical and psychosocial impairments, including increased risk of cardiovascular disease, psychiatric disorders, and cognitive decline. Pharmacological treatment, although widely used, is still a matter of debate, especially in relation to efficacy, safety, and suitability for long-term use.

Benzodiazepines (BZD) and benzodiazepine receptor agonists, known as Z-drugs (zolpidem, zopiclone, and zaleplon), remain among the most commonly prescribed medications for the management of insomnia, due to their proven efficacy in reducing latency and increasing total sleep duration (Crescenzo et al., 2022). However, the continued use of these substances is related to important adverse effects, such as tolerance, dependence, cognitive impairment, residual sleepiness, and increased risk of falls, especially in elderly individuals (Schroeck et al., 2016; Hassinger et al., 2020). In view of these limitations, it is necessary to investigate therapeutic alternatives that reconcile clinical efficacy and safety, with less potential for dependence — in this context, melatonin stands out.

Melatonin is an endogenous hormone secreted by the pineal gland, fundamental in the regulation of the circadian rhythm and the sleep-wake cycle. The exogenous administration of this hormone has been widely studied as a therapeutic strategy for sleep disorders, including primary insomnia, due to its safety profile and the absence of potential for dependence (Auld et al., 2017; Kim; Yang, 2022). Recent studies and systematic reviews indicate that melatonin, particularly in extended-release formulations, is effective in reducing sleep latency and improving subjective quality of rest, although its effects may be more modest when compared to benzodiazepines (Wang et al., 2021; Park et al., 2023). Such results reinforce its role as a physiological and potentially safer alternative for the treatment of insomnia.

In addition to their direct use in the management of insomnia, melatonin and its agonists, such as ramelteon, have been shown to be useful in discontinuing benzodiazepines and other hypnotics. Recent research suggests that the administration of melatonin may facilitate the gradual withdrawal of these drugs, reducing withdrawal symptoms and

promoting the restoration of circadian rhythm (Morera-Fumero; Fernández-López; Abreu-González, 2020; Cardinali et al., 2016). Neurobiological evidence also points to a synergistic interaction between melatonin and GABAergic systems, enhancing their sedative effects in a physiological way and with a low risk of toxicity (Vigo; Cardinali, 2018). These properties make melatonin particularly promising in vulnerable populations, such as the elderly and patients with multiple comorbidities.

However, despite advances in the understanding of the effects of melatonin and its agonists, **controversies persist regarding its comparative efficacy in relation to benzodiazepines**, especially in the management of primary insomnia. The literature presents heterogeneous results, which highlights the need for critical and integrated analyses of the available evidence. **Given this scenario, this study aims to review the scientific evidence published between 2015 and 2025 on the use of melatonin in the treatment of primary insomnia compared to benzodiazepines**, with emphasis on aspects of efficacy, safety, and risk-benefit. To this end, publications indexed in recognized databases, such as PubMed, SciELO, and ScienceDirect, were considered, in order to offer an updated and reasoned synthesis that supports evidence-based clinical decisions.

## 2 METHODOLOGY

The present study consists of an **integrative literature review**, of a descriptive and exploratory nature, elaborated according to the methodological guidelines proposed by **Whittemore and Knafl (2005)** and based on the principles of scientific research described by **Gil (2019)** and **Lakatos and Marconi (2017)**. This type of review aims to gather, evaluate, and synthesize in a systematic and critical manner the results of previous research, allowing a comprehensive understanding of the current state of scientific knowledge regarding a given phenomenon. In the present case, the focus is on the use of melatonin in the treatment of primary insomnia compared to benzodiazepines.

The preparation of this review was guided by the following **research question**: *does melatonin have comparable or superior efficacy and safety to benzodiazepines in the treatment of primary insomnia?* This question was structured according to the **PICO** strategy, in which P represents the population composed of adults diagnosed with primary insomnia; I refers to the intervention, defined as the use of melatonin or melatoninergic agonists; C corresponds to the comparison with benzodiazepines and Z-drugs (zolpidem, zopiclone and

zaleplon); and O designates outcomes related to therapeutic efficacy, safety, tolerability, and risk-benefit profile.

The **bibliographic search** was carried out between January and October 2025 in the **PubMed**, **SciELO, ScienceDirect** and **Scopus databases**, internationally recognized for the quality and scope of indexing of scientific journals in the health area. Controlled descriptors and free terms in Portuguese and English were used, according to the vocabularies **DeCS** (Health Sciences Descriptors) and **MeSH** (Medical Subject Headings), combined by the Boolean operators *AND* and *OR*. The descriptors used were: *"melatonin*", *"melatonin agonists*", *"primary insomnia", "sleep disorders", "benzodiazepines", "Z-drugs", "hypnotics", "efficacy"* and *"safety".* Filters were applied to limit the search to studies published between **2015 and 2025**, available in full text, peer-reviewed, and written in Portuguese, English, or Spanish.

Original studies, randomized controlled trials, systematic reviews, meta-analyses, narrative reviews, and clinical guidelines addressing the use of melatonin or its agonists (such as ramelteon, agomelatine, and tasimelteone) in the treatment of primary insomnia were included, as well as comparisons with benzodiazepines and Z-drugs. Studies carried out with , which presented quantitative or qualitative results on efficacy, safety and tolerability, were considered eligible. Articles **adults (≥18 years old) dealing with secondary insomnia associated with other medical or psychiatric diseases, studies with animal models, brief communications, letters to the editor, case reports, abstracts of scientific events, and duplicate publications were excluded.**

The **screening of the studies** was conducted in three stages. Initially, **112 potentially relevant publications** were identified. After reading titles and abstracts, **64 studies were excluded** because they did not meet the inclusion criteria. Among the **remaining 48** articles, **28 were excluded** after complete reading because they had inadequate designs, incomplete data, or a divergent focus from the central theme. At the end of the process, **20 studies** were included in the final sample, all published between 2015 and 2025 in journals indexed in the consulted databases.

Data extracted from each study included the authors' names, year of publication, type of study, sample size, population characteristics, type of intervention, comparator, outcomes evaluated, and main results regarding the efficacy and safety of the drugs. The **analysis of the results** was conducted through a **qualitative synthesis of a thematic nature**, according to the method of **Bardin (2016),** which made it possible to identify emerging categories of

evidence related to therapeutic efficacy, tolerability, and risk-benefit of the drugs evaluated. The convergences and divergences between the findings were discussed in an interpretative way, prioritizing studies of greater methodological robustness, such as meta-analyses, systematic reviews and international clinical guidelines.

The **validation of the methodological quality** of the included studies was based on the criteria of hierarchy of evidence proposed by the **Oxford Centre for Evidence-Based Medicine (OCEBM, 2011),** attributing greater weight to systematic reviews and randomized clinical trials. The final synthesis was organized in order to provide a critical and updated view of the use of melatonin and its pharmacological comparisons, highlighting clinical implications and gaps in the literature.

The ten-year time restriction, the use of four specific databases, and the exclusion of studies not available in full text are recognized as a limitation of this review, which may have led to the loss of some relevant publications. Furthermore, the qualitative nature of the analysis does not allow statistical generalizations, but offers a consistent interpretative synthesis of the available evidence.

As this was a study that exclusively used secondary data obtained from public sources and already published, **there was no need to submit it to the Research Ethics Committee**, as provided for in **Resolution No. 510, of April 7, 2016**, of the **National Health Council (Brasil, 2016).**

## 3 RESULTS AND DISCUSSION

The present integrative review identified twenty relevant studies published between 2015 and 2025, covering controlled clinical trials, systematic reviews, meta-analyses, and international clinical guidelines that evaluated the efficacy and safety of melatonin and its melatoninergic agonists (ramelteon, agomelatine, and tasimelteon) compared to benzodiazepines and Z-drugs (zolpidem, zopiclone, and zaleplon) in the treatment of primary insomnia. Among the included studies, 14 reported positive clinical efficacy of melatonin, with a mean reduction in sleep latency between 7 and 15 minutes, nine highlighted significant improvement in subjective sleep quality, and five pointed to additional benefits in discontinuing hypnotics. Although the absolute efficacy of melatonin appears slightly lower than that of benzodiazepines in inducing sleep, evidence has demonstrated its superiority in safety, tolerability, and risk-benefit profile, especially in elderly populations and in long-term treatments.

The meta-analysis conducted by **Auld et al. (2017),** published in *Sleep Medicine Reviews*, demonstrated that melatonin supplementation reduced sleep onset time by an average of 9 minutes in adults with primary insomnia, in addition to increasing overall sleep efficiency by approximately 3%. These results were corroborated by the network meta-analysis by **Wang et al. (2021),** which compared 36 pharmacological agents and identified that melatonin and ramelteon had moderate performance in reducing sleep latency, but with a significantly lower incidence of adverse effects compared to benzodiazepines and Z-drugs. These findings indicate that, although melatonin does not promote sleep induction as quickly as classical hypnotics, it represents a safer alternative for prolonged use, with a low probability of causing dependence, tolerance, or cognitive impairment.

Benzodiazepines and Z-drugs continue to be considered effective in the treatment of short-term insomnia, due to their ability to reduce sleep latency and increase total rest time. However, systematic reviews and international guidelines warn of important risks associated with the prolonged use of these drugs. The review by **Schroeck et al. (2016),** published in *Clinical Therapeutics*, highlighted that chronic benzodiazepine use in the elderly is strongly related to cognitive impairment, daytime sleepiness, and increased risk of falls and fractures. Similarly, **Hassinger et al. (2020)** emphasized that the continuous use of these drugs for more than four weeks substantially increases the risk of dependence and withdrawal syndrome, reinforcing the need for caution and the search for safer pharmacological alternatives, such as extended-release melatonin.

In terms of safety, the literature presents a consensus that melatonin and its agonists have the best tolerability profile among the available hypnotics. The quantitative risk-benefit analysis carried out by **Cheung et al. (2023)** pointed out that melatonin was the agent with the lowest rate of adverse events, highlighting the absence of dependence, residual effects, or psychomotor impairment. Similarly, **Cardinali et al. (2016)** observed that the administration of melatonin can facilitate the gradual reduction of benzodiazepines, helping to interrupt the prolonged use of these drugs. In line with these findings, the study by **Morera-Fumero et al. (2020)** showed that patients in the process of discontinuing hypnotics had success rates between 64% and 78% when melatonin was used as an adjuvant therapy, indicating its relevance in the management of addiction and the restoration of circadian rhythm.

The role of melatonin in specific populations was also widely discussed. **Salahub et al. (2022),** in a review published in the *Journal of Clinical Medicine*, observed that melatonin

reduced the incidence of delirium, falls, and sleep disorders in hospitalized patients, making it a safe therapeutic option for use in a clinical setting. Similarly, the clinical trial conducted by **Park et al. (2023)** demonstrated that administering extended-release melatonin (2 mg) significantly improved sleep quality and overall well-being in older adults with primary insomnia with no report of serious adverse events. These data suggest that melatonin may be particularly beneficial in vulnerable populations, such as the elderly and polymedicated patients, in whom benzodiazepines increase the risk of drug interactions and falls.

Although the hypnotic efficacy of melatonin is inferior to that of benzodiazepines in the short term, its circadian rhythm modulating action, combined with the absence of dependence and tolerance, justifies its use as a first-line treatment for mild to moderate cases of primary insomnia. According to **Riemann et al. (2017),** in a European guideline on the management of insomnia, the use of melatonin and melatoninergic agonists is recommended when pharmacotherapy becomes necessary, especially in the elderly and patients with a history of long-term use of hypnotics. This position is reinforced by **Crescenzo et al. (2022),** who indicated in a meta-analysis published in *The Lancet* that melatonin has a higher risk-benefit ratio than benzodiazepines, particularly in long-term treatments.

Despite the predominance of results favorable to melatonin, some studies have presented methodological limitations that restrict the generalization of the findings. Among them, small samples, heterogeneity in the doses and formulations used, short duration of the tests and absence of objective sleep measures, such as polysomnography, stand out. These limitations were observed, for example, in some studies included in the meta-analyses by **Auld et al. (2017)** and **Wang et al. (2021).** Such factors may explain the variability of the results and the divergences found between different revisions. Even so, there is **consensus regarding the safety and tolerability of melatonin**, reinforcing its clinical value as a lower-risk alternative compared to benzodiazepines.

Overall, the evidence analyzed points to a **trend of gradual transition from the use of benzodiazepines to melatoninergic drugs**, driven by concerns about safety, dependence, and adverse effects. Studies such as those by **Atkin et al. (2018)** and **Vigo and Cardinali (2018)** reinforce that melatonin, ramelteon, and agomelatine have mechanisms of action that mimic the natural circadian cycle, resulting in improved sleep quality without significant interference in cognitive functions. In addition, there is evidence that melatonin acts synergistically with the GABAergic system, reducing neuronal

hyperarousal associated with insomnia, which contributes to its long-term safety and efficacy profile.

In general, the findings of this review indicate that, although benzodiazepines maintain greater hypnotic potency in the short term, melatonin and its agonists are effective and safe alternatives, with consistent benefits in tolerability and absence of dependence. These results have relevant clinical implications, especially in the management of primary insomnia in the elderly, in the discontinuation of hypnotics, and in the promotion of more physiological and sustainable therapies. However, it is recommended that future research include clinical trials of longer duration and larger samples, with standardization of formulations and objective outcomes, in order to strengthen the evidence base and consolidate clinical guidelines based on robust results.

## 4 CONCLUSION

The present integrative literature review allowed us to critically analyze the most recent scientific evidence, published between 2015 and 2025, on the use of melatonin and its melatoninergic agonists in the treatment of primary insomnia, in comparison with benzodiazepines and Z-drugs. Thus, in response to the guiding question of this study, it is concluded that melatonin has similar therapeutic efficacy, although slightly inferior to that of benzodiazepines in inducing sleep, but with a significantly higher safety and tolerability profile.

Evidence indicates that melatonin is effective in reducing sleep latency and improving the subjective quality of rest, standing out for the absence of dependence, tolerance and cognitive impairment. On the other hand, the continued use of benzodiazepines is associated with relevant adverse effects, such as dependence, tolerance, cognitive impairment, and increased risk of falls, which limits their use in prolonged treatments. These findings reinforce the role of melatonin as a preferred therapeutic option in mild to moderate cases of primary insomnia and in at-risk populations, such as the elderly and polymedicated patients.

This review contributes to clinical practice by gathering and synthesizing the most up-to-date evidence on the efficacy and safety of melatonin, offering subsidies for therapeutic decisions based on evidence-based medicine. In clinical practice, it is recommended that extended-release melatonin be considered as the first pharmacological option in patients who do not obtain a satisfactory response to nonpharmacological interventions, or in those in whom the use of benzodiazepines represents an increased risk of adverse events. In

addition, its use may be beneficial as an auxiliary strategy in the discontinuation of hypnotics and benzodiazepines, favoring a safe and physiological therapeutic transition.

As a limitation, it is recognized that this review was restricted to publications available in four databases (PubMed, SciELO, ScienceDirect, and Scopus) and to the period from 2015 to 2025, which may have led to the exclusion of relevant studies that were not indexed or prior to this time frame. Furthermore, the qualitative nature of the analysis does not allow statistical generalizations, but provides a consistent and integrated interpretative synthesis of the available scientific evidence.

In summary, the consolidation of the clinical use of melatonin as a therapeutic alternative to traditional hypnotic pharmacotherapy represents a significant advance in the approach to primary insomnia, promoting safer, physiological, and more sustainable practices. The expansion of controlled and long-term research on specific doses, formulations and populations can strengthen the existing evidence base and consolidate melatonin as a reference agent in the modern treatment of insomnia.

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