

Review

Pharmacological Treatment of Primary Insomnia in Senior Citizens in Spain: A Comprehensive Analysis

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Abstract: The article examines the problem of primary insomnia in older adults in Spain, focusing on its prevalence and health consequences. It highlights that, unlike secondary insomnia, primary insomnia has no identifiable cause and may be related to factors such as stress, emotional distress, travel and shift work. Using data from the Spanish National Institute of Statistics, the prevalence of insomnia in older adults is analysed, highlighting a higher incidence in women and the 75+ age group. The importance of addressing this problem is emphasised, as insomnia in older adults is associated with serious consequences such as depressive episodes, increased risk of falls, cognitive impairment and reduced quality of life. The study aims to comprehensively examine the management of primary insomnia in this population, evaluating the efficacy of various pharmacological treatments, such as cognitive behavioural therapy, benzodiazepines, benzodiazepine receptor agonists (Z-drugs), antidepressants, melatonin and other options. The pros and cons of each treatment are discussed, including special considerations for older adults. This highlights the importance of future research to improve the understanding and management of chronic insomnia, underlining the need for large-scale studies of high methodological quality to establish appropriate pharmacological management.

Key words: Sleep Initiation and Maintenance Disorders, Aged, Drug Therapy, Cognitive Behavioral Therapy, Hypnotics and Sedatives, Z-drugs, Antidepressive Agents, Melatonin, Mindfulness, Pregabalin.

1. Introduction

The fundamental manifestations of primary insomnia consist of challenges in initiating or maintaining sleep, or the manifestation of agitated sleep that endures for a minimum of one month. Unlike secondary insomnia, which is a symptom or side effect of another problem, primary insomnia has no other identifiable cause. The origin of this is not well understood, but long-term stress, emotional distress, travel, and shift work might contribute to it.

Depending on age, sleep needs vary. As one gets older, the amount of sleep needed tends to decrease [1], with nighttime awakenings becoming more common, averaging 1 to 3 awakenings in young adults and 3 to 4 in older adults.

According to data from the National Statistics Institute (INE) in Spain, the prevalence of insomnia varies according to age and sex, with a higher percentage of difficulty falling asleep and frequent awakenings in the 75+ age group, reflecting the importance of addressing the problem of insomnia in the older adult population [2].

Insomnia, especially in older adults, is a significant health problem that can have serious consequences. Research has shown that disturbances in sleep may act as a catalyst for depressive episodes [3,4], amplify the likelihood of falls, deteriorate cognitive performance (specifically in the areas of concentration and retention), impede motor responses, and lower quality of life [5].

In addition, insomnia in older adults is often a secondary symptom of an illness or medication, which adds a layer of complexity to the diagnosis and treatment. Therefore, it is crucial to research and better understand this disorder to improve the quality of life of senior citizens and reduce the burden on the healthcare system.

1.1. Aims of the research

The primary objective of this inquiry is to comprehensively examine the administration of primary insomnia in senior citizens through medication in Spain. In pursuance of this goal, the ensuing specific objectives have been identified:

1. By analyzing data, this study will determine the prevalence of insomnia in the older adult demographic in Spain and provide a better understanding of this significant health issue.
2. Impact of insomnia on the physical and mental health of Older Adults: This study will examine how insomnia affects their physical and psychological well-being, including their quality of life and daily functioning.
3. Analyzing Pharmacological Treatments for Insomnia in the Senior Population: This study will scrutinize various therapeutic methods for managing insomnia in older adults, according to the most recent Guidelines and recommendations. The matter of treatment options will be explored, including Cognitive Behavioral Therapy (CBT), benzodiazepines (BZD), BZD receptor agonists (Z-drugs), antidepressants, pregabalin, melatonin, and other treatments such as phytotherapy and Mindfulness therapy. The pros and cons of each option will be discussed, along with special considerations for their use in the older adult population.
4. Discuss special treatment considerations.
5. Summarize the findings and provide management recommendations for medical practice and future research.

By addressing this perspective, this study aims to improve the understanding and management of primary insomnia in older adults in Spain.

2. Biological architecture of sleep

The biological structure of sleep consists of various stages that repeat during the night (Figure 1). The initial phase of sleep, known as light sleep, encompasses stages 1 and 2 of the sleep cycle [6]. These stages are distinguished by a decrease in cerebral function compared to wakefulness and serve as an intermediary stage between wakefulness and profound slumber. Slow wave sleep, also known as delta sleep, occurs during phases 3 and 4 of deep slumber, during which the brain activity declines and the body focuses on repairing and rejuvenating itself. The last segment of sleep, known as the phenomenon of Rapid Eye Movement (REM) sleep, is when the brain exhibits wakefulness-like activity and is the prime time for dreaming [6]. During REM sleep, the body experiences temporary paralysis, which prevents the movements that occur in dreams from taking place in reality. This sleep cycle is repeated several times throughout the night, with periods of REM sleep lengthening as the night progresses. Disrupting REM sleep can hinder your ability to process new information and emotions [7], as it is vital for memory consolidation and learning [8,9]. One of the fundamental aspects of assessing sleep quality is sleep efficiency. Sleep efficiency refers to the proportion of time a person spends sleeping about the total time spent in bed. The calculation presented herewith establishes the ratio by dividing the aggregate duration of rest by the entire timeframe occupied in the bed and subsequently multiplying the quotient by 100 [10]. A high sleep efficiency is a sign of good sleep, while a low sleep efficiency could point to sleep issues like insomnia.

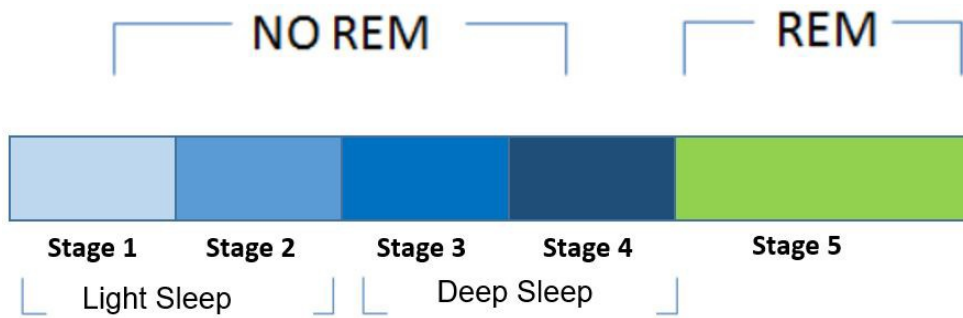


Figure 1. Representation of the different phases of the sleep cycle.

Depending on age, sleep needs vary. The recommended amount of sleep for adults is 7–9 hours, although individual demands may differ. The older we get, the less sleep we typically need, and adults over 65 years usually require 7 to 8 hours of sleep. Sleep latency, i.e. the time it takes to fall asleep, should not exceed 30 minutes. While consistent sleep is preferred, it is usual to have interrupted sleep as we grow, with young adults typically waking 1 to 3 times and older adults waking 3 to 4 times. As for naps, they are dispensable from the age of 5 years onwards, as they can interfere with nighttime sleep.

This sleep disorder is common and can affect people of any age, although it is more common in older adults.

3. Definition of adulthood and old age in Spain

It is important to note that in Spain, the attainment of 18 years of age marks the point at which individuals attain complete legal authority and can fulfil their obligations and entitlements as members of society. The term "adult" encompasses more than just reaching a certain age, as it also entails a set of qualities and duties that come with being mature and self-sufficient. As society and culture continue to evolve, the definition of adulthood is a topic that is constantly being reevaluated and discussed. Life expectancy for women has increased to around 80 years, leading to a growing number of older individuals within the overall ageing population.

At reaching 65, the Royal Spanish Academy (RAE) asserts that individuals enter the third stage of their lives [11]. Senior citizens are categorized into two groups by the INE: group 1 and group 2. These groups consist of individuals aged 65–74 and 75 years and above. The scope of this study includes individuals aged 65 years and above, divided into two distinct age categories.

3.1. Prevalence of insomnia in senior citizens in Spain

The ageing of the population is an evident phenomenon in Spain, with a prognosis of 30% by 2050.

Primary insomnia affects one-fifth of the population over 65 years of age in Spain. Its prevalence is significantly higher in women (27.2%) than men (11.4%).

To consult the primary data in the INE database [2], we considered the following search criteria: both genders, age stratification (Group 1: 65–74 years; Group 2: 75 or more years), and sleep problems (Figure 2). Sleep difficulties include three characteristic signs of insomnia such as difficulty falling asleep, repeated awakenings and early awakenings. Number of sleeping hours has been classified into the following ranges according to daily sleep recommendations: Range 1: < 6 hours and Range 2: 6–7 hours.

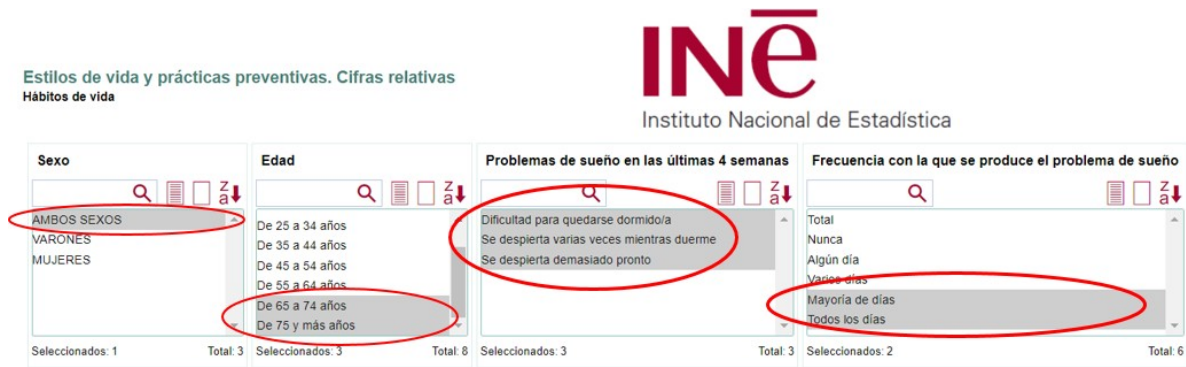


Figure 2. Sleep problems by sex and age group in the population over 16 years of age. Source: National Statistics Institute (INE) [2].

4. Impact of insomnia on senior citizens

The prevalence of sleep deprivation in older adults can significantly influence their overall health and quality of life. Sleep disturbances in this population can manifest themselves in various ways, including difficulty falling asleep, frequent nighttime awakenings and early morning awakenings (Table 1). The negative impacts of these sleep disruptions can include impaired memory, trouble with concentration and attention, mood swings, feeling drowsy during the day, decreased motivation and drive, a greater likelihood of making mistakes and having accidents [12], and experiencing physical symptoms such as tension [13], headaches [14], and gastrointestinal problems [15].

In addition, insomnia in older adults may be associated with an increased risk of mood disorders, such as depression, and with an increased risk of chronic diseases, such as diabetes [16], hypertension [17] and cardiovascular disease [18].

Evidence suggests that insomnia within this cohort could potentially contribute to a heightened probability of experiencing falls and dementia [19,20]. Insomnia can lead to adverse outcomes in older adults, including memory problems, lack of focus, and difficulties in social and professional interactions.

Table I. Main sleep disturbances in patients with insomnia.

Signs	Symptoms
Difficulty falling asleep	Difficulty sleeping
Difficulty concentrating	Memory difficulties
Frequent awakenings during the night	Daytime fatigue
Feeling of not resting properly	Irritability
Difficulty maintaining sleep	Attention problems
Restlessness before sleep and muscle tension	Anxiety and cognitive alterations

5. Treatment

5.1. Treatment approach in primary care

The treatment of primary insomnia is approached holistically, considering both the causes and the symptoms and their impact on the patient. The European Guideline states that Cognitive Behavioral Therapy (CBT) is the primary treatment for insomnia [21]. If CBT is not possible, an alternative therapy can be considered.

CBT is the first fundamental therapeutic step, regardless of the type of insomnia, and can be implemented in primary care or by referral to psychiatry.

5.2. Benzodiazepines (BZDs)

Should the need arise for prescription medication, benzodiazepines are the primary course of treatment for transient insomnia lasting no more than four weeks. The GABA-A receptor, responsible for inhibiting the central nervous system, includes the benzodiazepine receptor as one of its essential parts. By binding to a specific site on the GABA receptor, benzodiazepines increase the affinity of the GABA neurotransmitter [22], resulting in increased GABAergic inhibitory transmission (Figure 3). This increased inhibitory transmission leads to calming, sleep-inducing, relaxing, and anti-seizure effects.

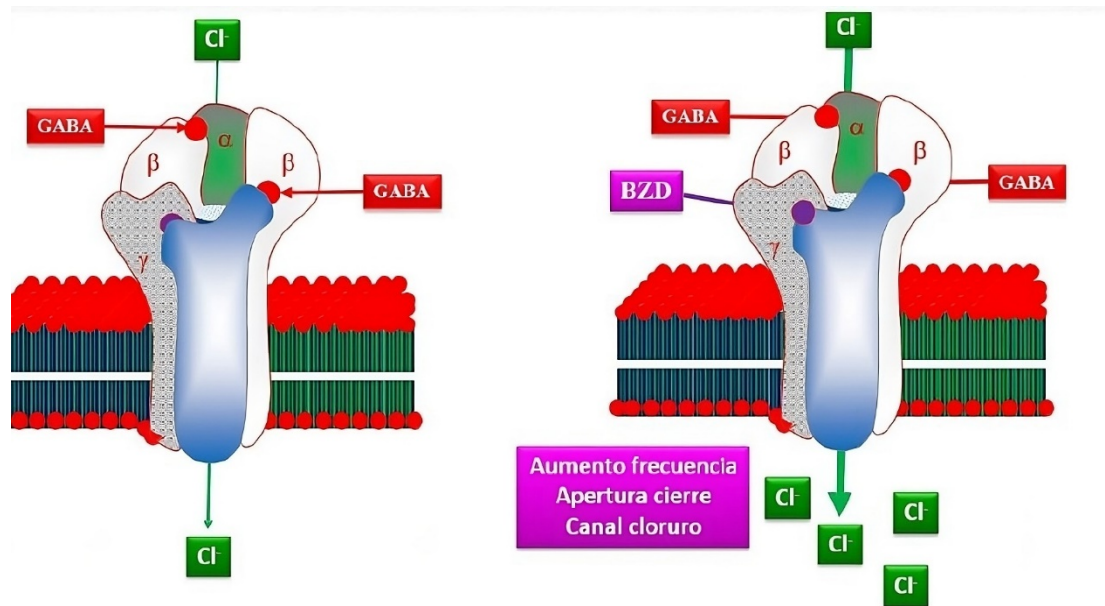


Figure 3. GABA receptor-benzodiazepine receptor complex chloride ionophore. Courtesy of Prof. Dr. Cecilio Álamo.

These particular drugs are intended for the brief management of anxiety and sleep disturbances in the elderly demographic. They are recommended for use at the minimum effective dose (MED) for the briefest period possible [23], not exceeding 30 days. When dealing with elderly individuals, it is advised to administer only half of the suggested dose. However, not all benzodiazepines have the same indications. The significance of their half-life and potential adverse effects (Figure 4) must be carefully considered.

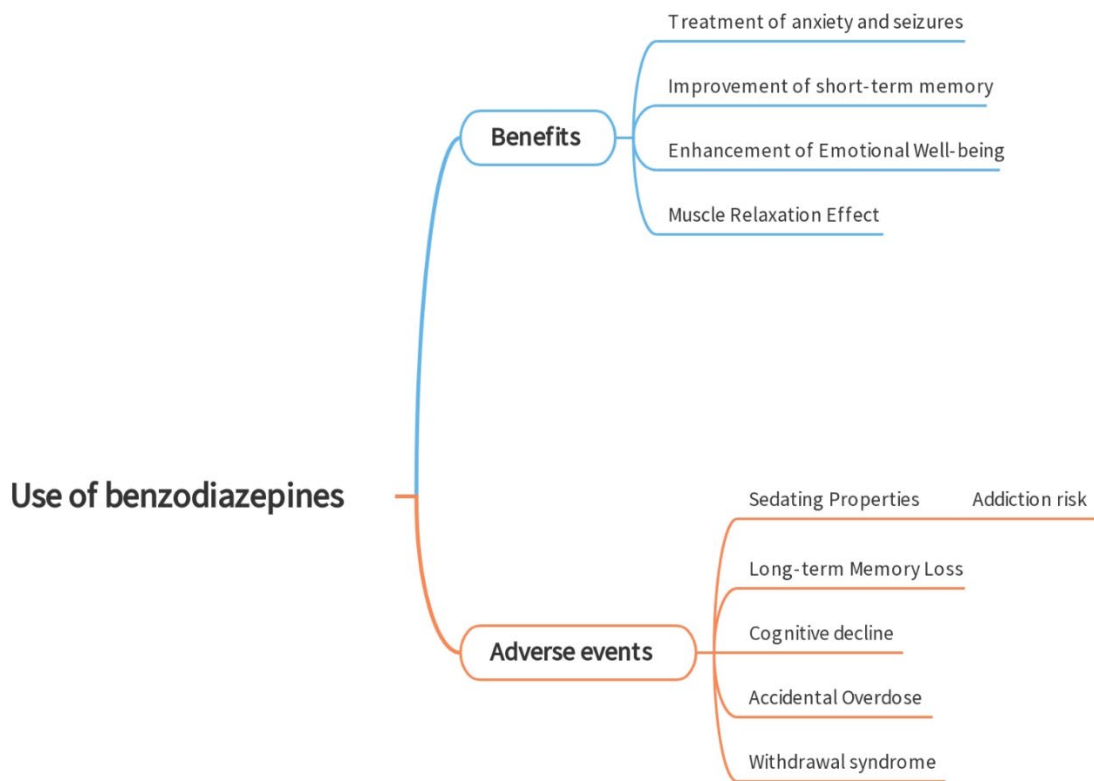


Figure 4. Common adverse effects of benzodiazepine administration.

5.3. Benzodiazepine Receptor Agonists (Z-drugs)

BZD receptor agonists, also known as Z-drugs, are effective in the short term for acute insomnia. Nonetheless, prolonged implementation is discouraged due to unfavourable outcomes and the acquisition of tolerance. Long-term use of Z-drugs may lead to adverse effects such as dependence, worsening insomnia, daytime sleepiness, confusion, and an increased risk of falls in older adults [23].

The Spanish Agency of Medicines and Medical Devices (AEMPS) has authorized zopiclone [24] and zolpidem [25] as Z drugs. Others, such as zaleplon and eszopiclone, are approved by the Food and Drug Administration (FDA) but have not been authorized for use by the AEMPS.

5.4. Antidepressive Agents

5.4.1. Tricyclic antidepressants

Tricyclic antidepressants such as doxepin are effective in the treatment of insomnia [26]. Notwithstanding, this indication is not encompassed in the technical data sheet of the pharmaceutical in Spain.

Trazodone has a significant hypnotic effect, which could help to improve sleep quality. Like doxepin, its primary use is to treat major depressive disorder. Furthermore, the use of it may lead to insomnia as a frequently encountered consequential effect.

5.4.2. Alpha2-adrenergic receptor antagonists

Mirtazapine is an α 2-adrenergic receptor antagonist that increases adrenergic neurotransmission at the presynaptic level. Like trazodone, it has a high hypnotic effect [27]. Insomnia does not fall under the outlined indications in the datasheet. In light of mirtazapine's effects, insomnia is supposed to be a markedly frequent adverse consequence.

5.5. Melatonin

Melatonin is a hormone produced naturally by the body, specifically by the pineal gland in the brain. This hormone plays a crucial role in regulating the body's circadian rhythms, which are cycles of sleep and wakefulness. Melatonin production increases in darkness and decreases in light, which tells the body when to be awake and when to sleep.

Melatonin has been used as a supplement to treat insomnia and improve sleep quality in a variety of conditions, such as jet lag. Research suggests that melatonin can reduce the time it takes to fall asleep, increase total sleep time and improve sleep quality [28,29].

The appropriate dosage of melatonin may differ from person to person. In adults, the typical dose used in studies varies from 1 to 10 mg [30]. The safe dose of melatonin is the lowest dose that effectively helps you sleep without causing any side effects. A safe initial dose is within the range of

0.2 and 5 mg. The current recommendation for older adults is 5 mg per night and 1 mg per decade. Consuming less than 2 mg is viewed as a dietary supplement.

The use of melatonin is controversial, and its effectiveness is a topic of discussion. Furthermore, there is insufficient evidence on the use of melatonin in patients over 55 years of age [30,31]. Extensive studies are required to confirm the benefits of its use on the patient's sleep hygiene.

5.6. Melatonin agonist (Ramelteon)

It is a melatonin agonist. It works by decreasing sleep latency and increasing total sleep time without causing residual symptoms, dependence or withdrawal. Furthermore, it is taken orally, usually once daily, at least 30 minutes before bedtime. However, Ramelteon has controversial evidence and requires a prescription in doses higher than 2 mg [32].

5.7. Antihistamines and orexin antagonists

The effectiveness of antihistamines such as chlorpheniramine and doxylamine is not significant, and using them for extended periods is not recommended due to potential side effects such as daytime drowsiness and decreased mental sharpness.

In contrast, orexin receptor antagonists, including suvorexant and dadirorexant, have been identified as a viable solution for insomnia [33]. Furthermore, the European Medicines Agency (EMA) has given its approval for dadidorexant due to its ability to enhance sleep latency and efficiency, as demonstrated in clinical trials with minimal side effects [34]. However, current evidence on orexin antagonists is limited, and further studies are needed to determine their long-term efficacy and safety profile.

5.8. Phytotherapy and Mindfulness therapy

The proposition of employing mindfulness therapy as a feasible and successful option [35] for prolonged treatment has been put forth but warrants further validation before being endorsed. On the other hand, phytotherapy with valerian has not shown significant effects.

5.9. Pregabalin

Pregabalin is a drug that belongs to the anticonvulsant class and is used in the treatment of pain-related insomnia. It works by decreasing the amount of pain signals that damaged nerves in the body send to the brain, which can help relieve chronic pain and improve the quality of sleep. Pregabalin is effective in the treatment of peripheral neuropathic pain [36], a condition that can be associated with insomnia [37]. Furthermore, it has been noted that this medication can enhance overall slumber duration and effectiveness, as well as promote tranquil sleep, which could prove highly advantageous for individuals afflicted with pain-induced insomnia.

In terms of its mechanism of action, pregabalin acts on the central nervous system to control seizures and neuropathic pain [36]. Although the exact mechanism through which pregabalin exerts its analgesic and anti-epileptic effects is unknown, it is believed that it may reduce the release of

excitatory neurotransmitters in neurons, which may help to decrease the sensation of pain and improve sleep quality.

Significantly, though pregabalin may prove efficacious in addressing pain-associated insomnia, it may also entail adverse reactions such as vertigo, lethargy, visual impairment, emotional fluctuations, and withdrawal manifestations [38].

6. Discussion

The treatment of primary insomnia is a topic of great importance in clinical practice, and its comprehensive approach is essential to ensure the well-being of patients. The European Guideline highlights Cognitive Behavioral Therapy (CBT) as the principal option for the treatment of insomnia, underlining its effectiveness regardless of the type of insomnia. Benzodiazepines (BZD) are one of the therapeutic options for acute insomnia, and their mechanism of action via the benzodiazepine receptor has been proven to be effective in the short-term treatment of anxiety and insomnia in elderly patients. It is advisable to only use them at the Minimum Effective Dose (MED) and for the shortest duration possible to avoid potential negative impacts and the risk of dependency. On the other hand, BZD receptor agonists, known as Z-drugs, are effective in the short term for acute insomnia. Though there is a discouragement of prolonged application of such substances due to the chance of adverse repercussions and development of tolerance, it is imperative to carefully assess their prescription in every case. In addition, other therapeutic alternatives have been explored, such as tricyclic antidepressants, α 2-adrenergic receptor antagonists, pregabalin, melatonin, melatonin agonist (Ramelteon), antihistamines and orexin antagonists. Consider the advantages and factors of each option before deciding which is best for the patient's circumstances. The pharmacological treatment of chronic insomnia remains an ongoing research gap in patient management. In this regard, it is essential to highlight the importance of future research that can provide additional evidence on the efficacy and safety of these therapeutic approaches and their long-term impact on patient's quality of life. The development of large-scale studies of high methodological quality will be crucial to improving the management of insomnia and ensuring the well-being of patients.

7. Conclusions

Insomnia in older adults is a significant health problem that can have serious consequences. Sleep disturbances can trigger depressive episodes, increase the frequency of falls, worsen cognitive functioning (especially attention and memory), slow motor responses and decrease quality of life. In addition, insomnia in older adults is often a secondary symptom of an illness or medication, which adds a layer of complexity to diagnosis and treatment. Therefore, it is crucial to research and better understand this disorder to improve the quality of life of older adults and reduce the burden on the healthcare system.

The treatment of primary insomnia is approached holistically, considering both the causes and the symptoms and their impact on the patient. The European Guideline argues that Cognitive Behavioural Therapy (CBT) is the main option for the treatment of insomnia, but if it is not feasible, an alternative therapy can be offered. Pharmacological treatment of acute insomnia offers a wide variety. Benzodiazepines (BZDs) are the main therapeutic option for acute insomnia, but their long-term use is discouraged due to adverse effects and the development of tolerance. BZD receptor agonists, also known as Z-drugs, are effective in the short term for chronic insomnia, but their long-term use is not recommended for the same reasons. In addition, other therapeutic alternatives have been explored, such as tricyclic antidepressants, pregabalin, melatonin, melatonin agonist (Ramelteon), antihistamines and orexin antagonists. Each of these options has specific advantages and considerations, and their choice should be based on the individual assessment of each patient. In this regard, it is essential to highlight the importance of future research that can provide additional evidence on the efficacy and safety of these therapeutic options, as well as their long-term impact on patient's quality of life. The development of large-scale studies of high methodological quality will also be crucial to establishing appropriate pharmacological management for the treatment of chronic insomnia, which is still controversial.

Competing interests: The author has declared that no competing interests exist.

Abbreviations

The following abbreviations are used in this manuscript:

AEMPS: The Spanish Agency of Medicines and Medical Devices.

BZD/ BZDs: benzodiazepine / benzodiazepines. CBT: Cognitive Behavioral Therapy.

EMA: European Medicines Agency.

FDA: Food and Drug Administration.

GABA: gamma-aminobutyric acid.

INE: National Statistics Institute.

MED: Minimum Effective Dose.

RAE: Royal Spanish Academy.

REM: Rapid Eye Movement.

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