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Effects of zolpidem extended release in management of insomnia and poor sleep quality: An expert panel insights review

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Abstract

Background: Adequate sleep is important for both physical and mental well-being. Sleep-wake disorders have negative effects on cognitive functioning and causes maladaptive metabolic changes. Zolpidem effectively treats insomnia across patient populations.

Aim: To understand the role of zolpidem Extended Release (ER) in the management of insomnia in the real-world setting.

Methodology: A Focused Group Discussion was conducted with 11 experts from the field of psychiatry and neurology to discuss the current treatment goals and clinical experiences for the management of insomnia.

Results: About 25% of patients attending OPDs have insomnia. 10-20% of these patients have primary insomnia, and the remaining 80-90% have comorbid insomnia. The first step to diagnose insomnia detailed history taking regarding the lifestyle and work profile of the patients. Only 20-40% of patients discuss insomnia with their doctors. Zolpidem ER is preferred by experts due to its rapid onset of action, short half-life of 2.8 hrs, less next-day sedation, increase in stage 3 sleep duration, and no alteration in sleep architecture and REM sleep.

Conclusion: According to the experts Zolpidem ER may have a favourable tolerability profile with a low predilection to cause clinical residual effects, withdrawal, dependence, or tolerance. Zolpidem is a useful option to treat patients with insomnia associated with comorbid diseases.

Keywords: Insomnia, Zolpidem Extended Release (ER), poor sleep, sleep maintenance

Introduction

Adequate sleep is essential for physical and mental well-being. Sleep can adversely affect cognition, mood, memory, metabolism, and immune response^[1].

The ICD-11 criteria define insomnia as a sleep disorder characterized by difficulty in falling asleep and/or remaining asleep, or difficulty in going to sleep or getting enough sleep. Patients with insomnia complain of middle-of-the-night (MOTN) awakenings with difficulty in returning to sleep. In the data analyzed from the US National Health and Wellness Survey, MOTN awakenings without other insomnia symptoms were reported by 3.5% of respondents. A study conducted by Panda *et al* reported that around 8% of the healthy population complained of early morning awakening^[2, 3]. Patients with insomnia also complain of daytime distress or functional impairment in social, occupational, and/or other critical areas of routine function. Chronic insomnia is a clinical diagnosis characterized by (a) difficulty initiating or maintaining sleep, (b) inability to sleep in spite of having adequate opportunities for sleep, (c) experiencing negative daytime impact due to lack of sleep, and (d) sleep difficulty not explained by other sleep/medical disorders with symptoms occurring at least three nights per week during a period of at least 3 months^[1].

Sleep-wake disorders have negative effects on cognitive, emotional, and interpersonal functioning and can cause maladaptive metabolic changes. Sleep-wake disorders, related to alterations in specific metabolic pathways, might contribute to the association with other psychiatric disorders and medical conditions^[4]. Patients with comorbid diseases, such as chronic heart and/or lung diseases, can have difficulty in the maintenance of sleep^[5]. Insomnia in neurological disorders is attributed to multiple factors, which encompass physical and neuropsychiatric factors, behavioral patterns, and disruptions in the biological clock and circadian rhythm.

Bidirectional connections between neurological disorders and insomnia^[6].

Sleep is regulated by neurotransmitters like gamma-aminobutyric acid (GABA) and histamine. Increased GABA and decreased histamine release induce Non-Rapid Eye Movement Sleep (NREM). Orexin, produced in the hypothalamus, is a neuropeptide that has a role in maintaining wakefulness. Orexin changes the activity of neurotransmitters involved in the regulation of sleep/wake states. Sleep is also regulated by melatonin which is a hormone that plays a critical role in diurnal rhythms.⁷ Decreased melatonin production can also contribute to insomnia. Modulation of these chemicals is the rationale for the development and use of the current drugs used to treat insomnia. There are several drugs available to treat insomnia, such as Benzodiazepines, Non-Benzodiazepines, or Z drugs, such as zolpidem and Orexin Receptor antagonists. Zolpidem ER has been used to treat insomnia for the past few decades across patient populations.

Considering the wealth of data that is now available, it is prudent to review zolpidem ER against the backdrop of comorbidities in the patients and compare it with the older and newer drugs available to treat insomnia^[7].

Methodology

This comprehensive review explores the recommendations for the management of insomnia from a panel of expert psychiatrists and neurologists across India and examines the current clinical practices and treatment objectives. Additionally, the experts' insights on the obstacles and difficulties related to using zolpidem to treat insomnia and potential approaches to overcome these challenges are also discussed.

A Focused Group Discussion (FGD) was conducted in May 2024, with an expert panel of 11 expert psychiatrists and neurologists on the treatment of insomnia. In the FGD, the experts discussed the current treatment goals and individual clinical experiences for the management of insomnia.

A literature search across databases such as PUBMED, COCHRANE, and Google Scholar was conducted for articles with keywords such as "Insomnia", "Zolpidem ER", "Poor Sleep", and "Sleep maintenance". The current guidelines for Insomnia management were also critically reviewed, and a descriptive analysis of the literature and expert opinions is summarized below.

Prevalence of insomnia

About 10% of the adult population has insomnia disorder, and another 20% experience occasional insomnia symptoms.⁸ Women and older adults have been reported to be more vulnerable to insomnia. Insomnia often presents as a chronic condition and displays a 40% persistence rate over a 5-year period^[8].

Chronic primary insomnia affects approximately 10% of the population^[9].

The reported prevalence rates of insomnia range from 11 to 74.2% in neurodegenerative disorders, 20 to 37% in vascular diseases, 13.3 to 50% in inflammatory diseases, 28.9 to 74.4% in epilepsy, and nearly 70% in migraines^[6].

Expert opinion

Insomnia in Indian patients attending the outpatient department

Experts opined that about 25% of patients attending their outpatient practice have insomnia. Of these while about 10-20% of those patients have primary insomnia, and the remaining 80-90% have comorbid insomnia. In metro cities, young adults present with primary insomnia due to shift work. Among the symptoms of insomnia, delay in sleep onset and sleep maintenance are more common than middle-of-night awakenings.

The expert panel unanimously highlighted that the general population often ignores sleep issues. Experts mentioned that patients with headaches and epilepsy can have comorbid insomnia and that insomnia is a major cause of obesity, hypertension, diabetes, and insulin resistance. The experts mentioned that a significant proportion of the young population who work as shift workers develop insomnia due to their work schedules.

The issue of sleep maintenance in patients with comorbid disorders

Sleep disturbance is a prominent symptom in patients with depression and was formerly regarded as a main secondary manifestation of depression^[10]. Patients with depression have reduced slow-wave sleep and abnormalities of REM sleep^[11]. Sleep disorders are also associated with other psychiatric disorders, such as schizophrenia, post-traumatic stress disorder, and attention deficit hyperactivity disorder^[12]. Chronic insomnia and shortened sleep time, may be associated with the development of diabetes, hypertension, and cardiovascular disease^[13]. Insomnia is common in post-stroke patients, especially in those patients who have anxiety and depression^[14]. Patients with laryngopharyngeal reflux often experience insomnia, and the severity of reflux symptoms is related to the severity of insomnia^[15]. Insomnia may be a causal factor for peptic ulcer disease due to increased oxidative stress.¹⁶ Insufficient sleep induces a positive energy balance and leads to weight gain^[17]. Large community-based epidemiological studies have proved the association between symptoms of insomnia and long-term cardiovascular mortality, independent of identified risk factors.¹⁸ Pharmacotherapy of insomnia may help in better control of BP and assist in the treatment of high BP in patients with insomnia^[19]. The mechanisms implicated in comorbid disorders associated with insomnia include inflammatory, immunological, neuro-autonomic, endocrinological, genetic, and microbiome disturbances^[20].

Expert opinion

Experts opined that a substantial proportion of patients ignore insomnia symptoms and do not report them to their physicians. The experts agreed that insomnia when left untreated may become chronic and persistent disorder and can negatively impact patients' health & associated comorbid conditions.

The experts mentioned that acute or occasional or short-term insomnia is more common in patients with acute psychiatric illness, substance abuse, Parkinsonism, and dementia and comorbidities. Chronic insomnia patients have poor sleep hygiene, comorbid anxiety or stress, depression, and personality issues. As per the experts, it has been observed that almost 80% of patients with chronic insomnia have comorbid conditions.

The experts mentioned that in the age group between 18-60 years, insomnia is often attributed to poor work-life balance, such as in shift workers working late till 2 am. The experts

mentioned that physicians must be vigilant and must investigate their patients for comorbid psychiatric, neurological, and medical disorders.

Evaluation of patients with insomnia

Expert opinion

Experts opined that the first step to diagnose insomnia is taking a detailed history regarding the lifestyle and work profile of the patients. Questions regarding the duration of insomnia must be asked in order to assess the type of insomnia (acute or chronic insomnia). Common questions to ask during history taking are listed in Table 1.

Table 1: Questions for arriving at the diagnosis of insomnia during history taking

- How much time do you require before you fall asleep?
- How long do you sleep?
- How many times do you awaken at night?
- Do you awaken early in the morning and find it difficult to go back to sleep?
- Do you experience sleepiness during daytime?
- Have you observed impaired concentration at work?

The experts opined that patients often ignore their sleep issues and only about 20-40% of patients discuss insomnia with their doctors. The experts mentioned that an empathetic, detailed history-taking could elicit the issues underlying the cause of insomnia.

The experts mentioned that among the age group of 18-60 years, patients complain of insomnia due to work stress, relationship problems, stress due to academics, and usually present late after a couple of months, while patients who are >60 years, and females, visit early. The experts also opined that the majority of patients with insomnia have cognitive and memory problems.

The experts opined that rating scales and sleep scores are helpful to diagnose insomnia, especially for patients who understand them. Polysomnography is indicated only in patients who are comorbid with sleep apnea and other sleep disorders, along with insomnia.

Treatment of insomnia

The two primary objectives of the treatment of insomnia are the improvement of sleep quality and quantity. The initial approach to the treatment of insomnia includes non-pharmacological options such as stimulus control therapy, relaxation therapy, and biofeedback methods. If these measures do not help relieve insomnia, pharmacological treatment is recommended^[21]. Several factors must be considered when choosing a drug to treat insomnia (Table 2). One important aspect to consider when choosing a drug is to evaluate its effect on sleep architecture. Sleep is composed of 2 phases: Rapid Eye Movement sleep (REM) and Non-REM sleep (NREM). The NREM phase further consists of 3 stages:

Stage 1: Which is a transition from being awake to falling asleep;

Stage 2: Is the period of light sleep during which the eye movements stop;

Stage 3: Also called Slow Wave Sleep, is the period of deep sleep (SWS)^[22, 23].

Table 2: Factors to consider when choosing a drug to treat insomnia⁷

- Symptom pattern
- Treatment goals
- Desired onset and duration of action
- Past treatment responses
- Patient preference
- Comorbid conditions
- Contraindications
- Concurrent medication interactions
- Potential adverse effects
- Potential for abuse
- Potential for development of tolerance
- Cost

Overview of effects of zolpidem on sleep architecture and management of insomnia

Zolpidem is a non-benzodiazepine benzodiazepine GABA-A receptor agonist of the imidazopyridine class that is approved for the short-term treatment of insomnia. Unlike benzodiazepines, zolpidem binds preferentially and with high affinity to the BZ1 receptor (which corresponds to the alpha 1 subunit of the receptor complex) responsible for mediating the hypnotic effects of the drug^[24, 25].

Zolpidem was the first US FDA-approved non-benzodiazepine, benzodiazepine receptor agonist (non-BZD, or BzRA) hypnotic, which became available in 1992. zolpidem accounts for 87.5% of all BzRA prescriptions^[24, 25]. Zolpidem ER significantly lengthens slow-wave sleep (SWS; NREM stage 3), reduces the number of nocturnal awakenings and improves subjective sleep quality. (Figure 2) It has the advantage of causing minimal next-morning residual effects^[26].

Current evidence indicates that zolpidem IR and ER do not have any significant effect on variables such as driving, mood, affectivity, morning wakefulness and freshness. Zolpidem ER does not adversely affect attention, concentration, numerical memory, fine motor activity, and reaction time measures^[7, 27]. It causes a significant improvement in objective sleep quality by increasing total sleep period (TSP), total sleep time (TST), and sleep efficiency and shortening sleep latency^[7, 27]. Thus, Zolpidem ER helps in normalizing the disorder of initiating and maintaining sleep.

Expert opinion

Treatment of insomnia in Indian patients

The experts opined that patients often visit primary care physicians first for treatment of sleep issues, whereas usually, when a patient consults a psychiatrist, there can be a delay of up to 6 months to 1 year since the onset of symptoms. Patients often have already experimented with home remedies or alternative therapies before they come to the experts for treatment of insomnia.

The experts opined that non-pharmacological approaches and sleep hygiene tips, including prayers, relaxation techniques, lying down without stress, reading, and reduction of screen time before sleeping, are advised to the patient before initiating pharmacotherapy for insomnia.

Sleep relaxation, sleep hygiene, and regular exercise in the form of morning walks are the preferred sleep behavior therapies.

Cognitive Behavioral Therapy for Insomnia (CBTI) has been recommended by guidelines as a first line of treatment; it is not practiced routinely.

While choosing a drug to treat insomnia, associated comorbidities and the age of the patient are crucial factors to be considered, and if the patient is suffering from chronic diseases like multiple sclerosis, stroke, or myocardial infarction, their effects on cognition should be kept in mind. Before the development of Z drugs like zolpidem, experts cited instances of long-term use of benzodiazepines (BDZ) like alprazolam for their patients with ischemic heart disease. However, the experts mentioned that their patients would often continue to take the benzodiazepine for many years in spite of advising them not to do so. General practitioners often treat insomnia with BDZs like alprazolam and clonazepam, even though they are not approved for the treatment of insomnia in India. BDZs are habit-forming, develop tolerance, and have the highest risk of dependence and addiction. In elderly patients, muscle relaxation due to BDZ can lead to falls and respiratory depression. BDZ causes high daytime sedation in patients due to its exceedingly long half-life, and BDZ causes cognitive impairment in patients. Another challenge is self-medication by the patients with over-the-counter medications like melatonin.

The experts highlighted the advantages of zolpidem over BDZs, which include Zolpidem's selective action on GABA alpha 1 receptor, shorter half-life, minimal next-day sedation and impairment, increased stage 3 sleep duration, and no alteration in sleep architecture and REM sleep. The experts preferred adopting a combination of therapies to treat insomnia in their patients. Initially, they prefer to educate the patient about sleep hygiene, followed by pharmacotherapy

with zolpidem ER for sleep maintenance issues. In primary insomnia cases, they prefer both CBT I and zolpidem together. The experts opined that based on the efficacy of Zolpidem ER, it can be preferred as a first-line drug option for the management of insomnia, as recommended by various guidelines.

Some patients treated with newer drugs like Lemborexant have complained of daytime drowsiness and sedation, which is similar to the findings reported in the SUNRISE 1 and 2 clinical trials of Lemborexant. Lemborexant induces sleep for at least 8 hours, owing to its longer half-life of 17 to 18 hrs, which is why they feel sedated and drowsy during the day after waking up. Lemborexant can be considered as a second-line treatment option for insomnia management owing to its excessive cost, next-day sedation and drowsiness.

Development of zolpidem ER^[28]

Zolpidem tartrate extended-release (ER) 12.5 mg was developed to prolong the duration of action of the zolpidem IR formulation. It was developed as a dual-layered tablet that provides a biphasic release of zolpidem: an initial release of the drug to facilitate sleep onset and a delayed release to benefit the maintenance of sleep throughout the middle of the night. Zolpidem ER and the conventional zolpidem IR share similar rapid onsets of peak plasma concentrations (T_{max} : 1.5 h vs. 0.88 h, respectively) and elimination half-lives ($T_{1/2}$: 2.8 h vs. 2.6 h, respectively). Zolpidem ER exhibits higher, prolonged plasma concentrations than zolpidem IR beyond 3 h post-dose.(Figure 1). Zolpidem ER may have a favorable tolerability profile with a low predilection to cause clinical residual effects, withdrawal, dependence, or tolerance.²⁹It can also be an effective and useful option to treat patients with insomnia associated with comorbid diseases. Due to the efficacy of Zolpidem ER, it can be preferred as a first-line drug option for the management of insomnia^[29].

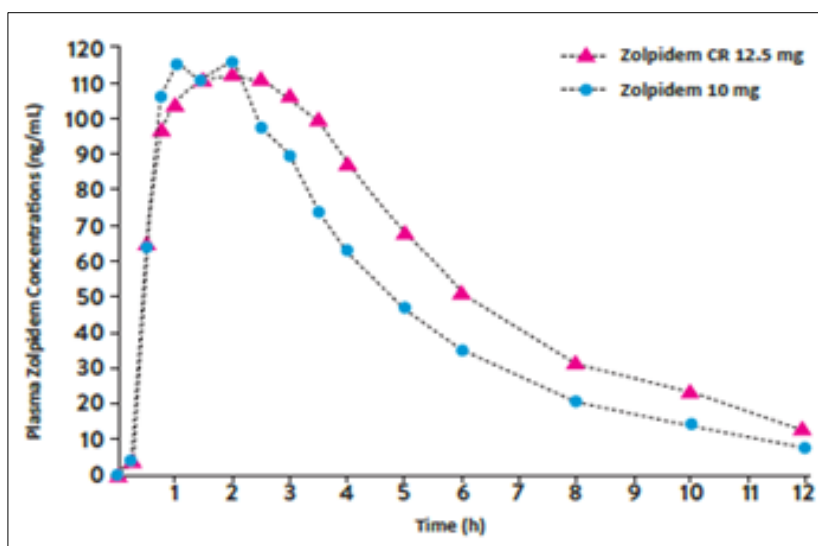


Fig 1: Biphasic Release profile of zolpidem ER/(CR: Controlled Release), which ensures sleep maintenance throughout the night

The recommended starting dose of zolpidem ER is 12.5 mg by mouth immediately before bedtime for the average adult patient. A lower dose of 6.25 mg is suggested for the elderly, women, and patients with debilitation or hepatic insufficiency^[30].

Expert opinion: Experts opined that short sleep onset latency, sleep maintenance for 6 to 7 hours, and prevention of

early morning awakenings are the most important goals of management of insomnia. NREM stage 3 is the most important for maintaining sleep architecture.

Zolpidem ER is a Bi-layered tablet; one-layer releases immediately (66% of the drug is released within 30 mins), while the other (34%) provides a slower and sustained release of additional zolpidem throughout the night. It is indicated for the management of insomnia, characterized by difficulties

with sleep onset and/or sleep maintenance. It has a tolerability profile similar to zolpidem immediate-release formulation^[30]. In patients complaining of sleep onset and maintenance issues, the experts prefer to use short-acting drugs such as Zolpidem IR for sleep onset and Zolpidem ER for sleep maintenance. When the problem is the initiation and maintenance of sleep in patients who need to work during the daytime, Zolpidem ER can be prescribed in all adult age groups. The chances of Zolpidem ER causing daytime sedation are minimal because of its biphasic release pattern and short half-life, and in students and the working population, Zolpidem ER can be a preferred treatment option. The experts agreed that zolpidem ER helps to treat insomnia without disturbing the sleep architecture, and it increases slow-wave sleep, thus ensuring that the patient does not have a hangover effect the next day. Zolpidem ER may have a favorable tolerability profile with a low predilection to cause clinical residual effects, withdrawal, dependence, or tolerance. Experts recommend initiating treatment of insomnia with 12.5 mg Zolpidem ER in patients between 18-

60 years, shift workers, while in elderly patients of >60 years and in women, they prefer to use 6.25 mg of Zolpidem ER to avoid the risk of falls. In co-morbid conditions, they usually initiate treatment with 6.25 mg and gradually increase the dose as required. Zolpidem IR and ER can be prescribed for 1 month and depending on the patient's profile and comorbid conditions as per the clinician's discretion, the duration can be extended.

Zolpidem ER can be preferred in patients with anxiety and depression for Insomnia management, and in such patients, initially, BDZs can be used to decrease anxiety symptoms, and then the patients can be switched over to Zolpidem for insomnia management.

Patients who have been taking long-acting BDZs for a long time should be tapered down slowly and shifted to Zolpidem IR/ER, and these patients don't complain after switching to Zolpidem, as it has dual benefits of sleep initiation and maintenance.

Zolpidem ER (CR) reduces night-time awakening by 50%.^[31] (Figure 2).

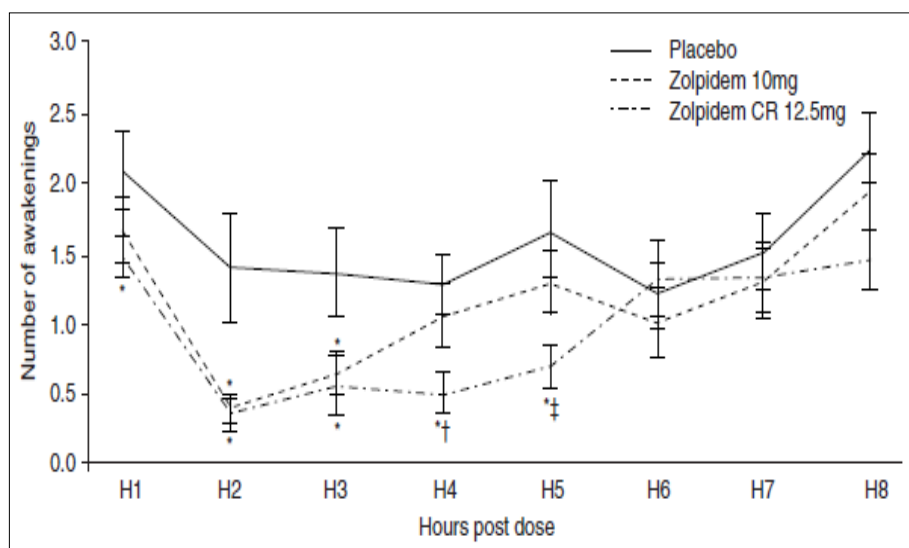
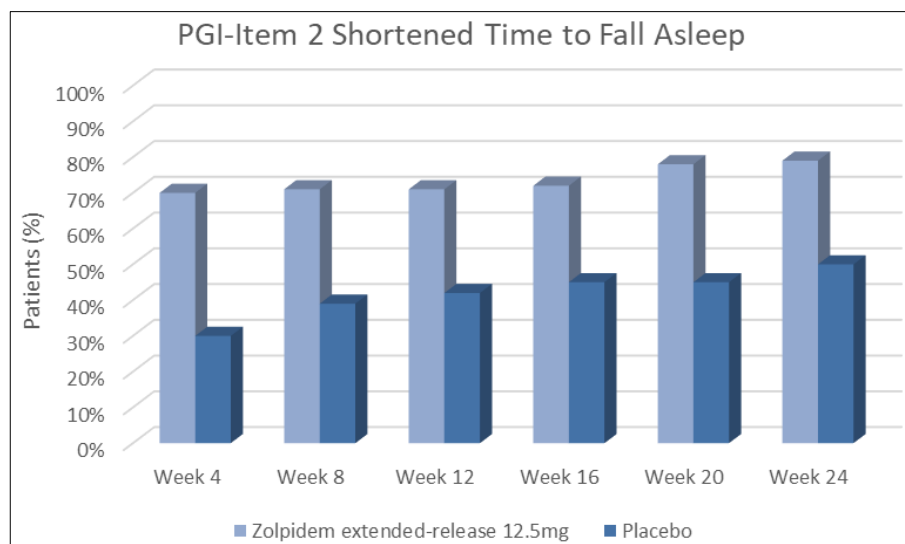


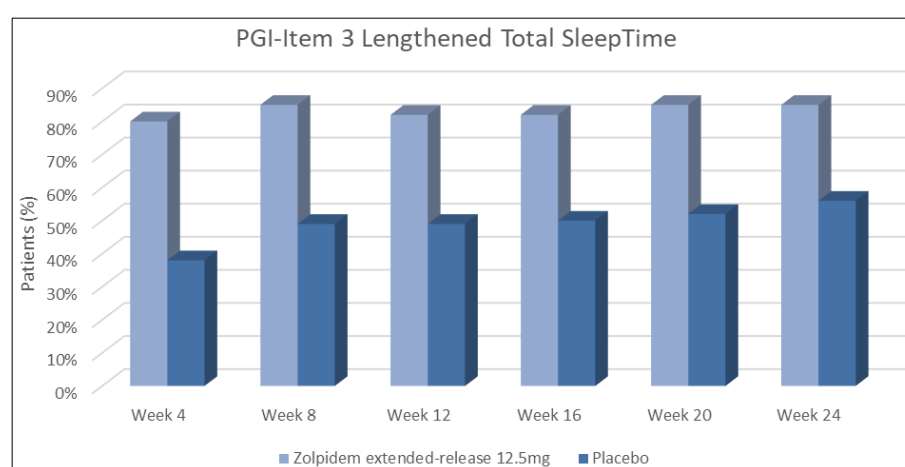
Fig 2: Effects of zolpidem controlled-release (CR) on the number of nocturnal awakenings in healthy volunteers^[27]

A study reported that patients treated with zolpidem were able to wake up easily and have been reported to have similar levels of alertness and contentment as placebo while no major adverse residual effects occurred the next morning^[32, 27]. In adult patients with primary insomnia who were treated with nightly administration of zolpidem, the polysomnographic evaluation indicated that, in comparison with placebo, zolpidem ER 12.5 mg significantly improved sleep onset latency, significantly reduced the duration of wake time after sleep onset (WASO) and the number of awakenings (NAW), both measures of sleep maintenance, on the first 2 nights of treatment and after 2 weeks of treatment^[9]. Several studies have demonstrated that sequential treatment, starting with behavioral therapy and subsequently zolpidem ER, results in greater response and remission over the longer term (1 year), indicating that this could be a more effective strategy for insomnia management^[34]. A multicenter, 25-week, phase III b, randomized, double-blind, placebo-controlled, parallel-group study by Krystal^[9], in adults with chronic primary

insomnia, proved the efficacy of 3 to 7 nights per week dosing of zolpidem extended-release 12.5 mg (N=669) for up to 6 months. At week 12, 89.8% of zolpidem patients vs. 51.4% of placebo patients reported their treatment helped them sleep in the Patient's Global Impression (PGI) scores. At week 24, 92.3% of zolpidem extended-release patients vs. 59.7% of placebo patients reported improved sleep. Sustained improvement was reported in morning sleepiness and ability to concentrate ($P=0.0014$, month 6) with zolpidem extended-release as compared with placebo. Zolpidem ER was significantly superior to placebo at every time point for PGI (Items 1-4) and Clinical Global Impression-Improvement (CGI-I) ($p<0.0001$, rank score), total sleep time (TST), wake time after sleep onset (WASO), quality of sleep (QOS), next-day functioning ($p<0.0001$), sleep onset latency (SOL) ($p<0.0014$); number of awakenings (NAW) (Months 2-6; $p<0.0001$). No rebound effect was reported during the first 3 nights of discontinuation^[9] (Figure 3).



A: Shortened time to fall asleep



B: Lengthened total sleep time

Fig 3: Improvements in PGI scores over 6 months of treatment with zolpidem ER versus placebo

In the double-blind, placebo-controlled study by Roth T, 212 patients with primary insomnia were randomized to 3 weeks of nightly treatment with either zolpidem-ER 12.5 mg or placebo, preceded and followed by two nights of single-blind placebo [35]. As compared to placebo, zolpidem ER 12.5 mg improved sleep maintenance by significantly reducing PSG (polysomnography) wake time after sleep onset (WASO) during the first six hours of sleep and also reduced the number of awakenings. Zolpidem ER significantly reduced latency to persistent sleep and significantly increased sleep efficiency, both at the beginning and after 2 weeks of treatment. The patients had no next-day residual effects. Rebound insomnia on the first night after abrupt discontinuation resolved the following night, and the drug was well tolerated [35].

Residual effects after treatment with zolpidem ER

Patients treated with zolpidem ER did not have a significant effect on vigilance, memory, or motor function, 8 hours post-nighttime dose in two placebo-controlled trials [30]. Within two placebo-controlled studies assessing patients with primary insomnia, after abrupt discontinuation of zolpidem ER, rebound insomnia was reported on the first night, while on the second night, symptoms were no worse than those reported at baseline [30].

Zolpidem ER in the management of insomnia in patients with comorbid diseases

Sleep disorders are common in patients with heart failure (HF), and caution is recommended when prescribing sedative-hypnotic drugs in this population, as they may cause depression of ventilation. Zolpidem ER has been demonstrated to be useful in such patient populations. In patients with heart failure (HF), zolpidem is the preferred drug to treat insomnia due to its low potential to cause respiratory depression [36]. In the study by Gatti *et al*, in 15 patients with heart failure and insomnia, a 16% increase in total sleep time was found with the use of zolpidem CR and an increase in stage 3 NREM sleep (slow wave sleep) was reported. Zolpidem CR improved sleep structure in patients with heart failure. The apnea-hypopnea index (AHI) did not change with zolpidem CR [36]. Zolpidem ER is effective in patients with comorbid disorders such as major depression, generalized anxiety disorder, chronic pain, and chronic medical conditions [37].

In elderly patients with insomnia, Zolpidem extended-release 6.25 mg improved both sleep maintenance and sleep induction during 3 weeks of administration [38]. However, unlike Zolpidem, benzodiazepines are associated with a higher risk of rehospitalization for HF compared with Z-drugs in patients with HF [39].

Expert opinion

The experts agreed that zolpidem ER is the preferred treatment option in patients of insomnia with comorbid diseases such as hypertension, diabetes, anxiety, depression, and migraine. As per the experts opinion, management of insomnia can also aid in managing the comorbid disease better, e.g., improved metabolic and glycemic control in patients with diabetes.

Conclusion

Zolpidem ER decreases sleep latency, decreases the number of midnight awakenings, and increases total sleep duration. It does not alter sleep architecture: it moderately increases stage 2, increases stages 3 (slow wave sleep), and does not decrease REM sleep. As per the experts Zolpidem ER may have a favorable tolerability profile with a low propensity to cause clinical residual effects, withdrawal, dependence, or tolerance. It can be an effective and useful option to treat patients with insomnia associated with comorbid diseases. The experts opined that based on the efficacy of Zolpidem ER, it can be preferred as a first-line drug option for the management of insomnia, as recommended by various guidelines.

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Declarations

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Conflict of Interest

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