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Review Article

Management of insomnia in India: expert consensus insights with a focus on zolpidem

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ABSTRACT

Insomnia is a global health concern affecting 10%-30% of the population. In India, the prevalence of insomnia among adults is 33%, with older adults being notably affected - urbanization, lifestyle changes, and increasing stress levels are factors that lead to insomnia. Despite its widespread impact, few people affected by insomnia seek treatment due to societal stigma and sparse data on the disorder. Benzodiazepines (BDZs), particularly alprazolam, which were once favored for insomnia treatment, are no longer recommended due to side effects, including addiction and dependence risks. Zolpidem, a selective agonist of BDZ (ω) receptors containing α-1 subunits, has emerged as a viable alternative, often used in conjunction with cognitive behavioral therapy (CBT). Currently, zolpidem is the preferred first-line pharmacotherapy for the treatment of insomnia as it does not alter sleep architecture, prevents daytime sleepiness, has a non-addictive nature, and its abrupt discontinuation does not induce dependence, withdrawal symptoms, or trigger rebound insomnia. This expert opinion manuscript aims to elucidate the treatment landscape for insomnia in India, with a focus on the use of zolpidem. Insights were derived from advisory board meetings involving 33 Indian physicians from diverse specialties. Discussions centered on the current status of insomnia in India, clinical experiences with zolpidem, and emerging pharmacotherapeutic options. In conclusion, valuable insights into the management of insomnia and related disorders, with a focus on pharmacotherapy using zolpidem, were gained. Zolpidem provides effective treatment when compared with BDZs and other drugs. However, it must be prescribed judiciously based on patient-specific factors.

Keywords: Cognitive behavioral therapy, Benzodiazepines, Insomnia, Zolpidem

INTRODUCTION

Background

Insomnia is characterized by difficulty falling asleep despite adequate opportunity and circumstances to sleep, frequent nocturnal or transient awakenings, and impairment of daytime functioning.[1,2] According to the clinical practice guidelines of the American Academy of Sleep Medicine (AASM), insomnia is identified as short-term if symptoms persist for <3 months and chronic if they persist for ≥3 months, with symptoms occurring at least three times per week.[3] Insomnia is primarily associated with physical, functional, emotional, and mental impairments.[4] The short-term effects of insomnia cause physical discomfort, fatigue, mood disturbances, and poor quality of life (QoL). Persistent insomnia results in mental health deterioration and the onset of various psychiatric conditions.[5]

Insomnia is highly prevalent worldwide, affecting a significant 10%–30% of the global population. In India, in 2016, the prevalence of insomnia was reported in 33% of adults, influenced by factors such as urbanization, lifestyle changes, and increasing stress levels.[6] A nationally representative longitudinal aging study conducted in 2018 in India revealed that 37% of older adults (>59 years of age) had insomnia, of whom only 3% sought treatment.[7]

Introduction to benzodiazepines and zolpidem

The preferred first-line treatment option for insomnia was benzodiazepines (BDZs); however, their use has declined due to side effects such as cognitive impairment and respiratory depression, along with dependence risk. Hence, BDZs such as temazepam and lorazepam are often reserved for short-term, refractory insomnia. Z-class drugs such as zolpidem, eszopiclone, and zaleplon are commonly prescribed as adjunct treatments for insomnia, along with cognitive behavioral therapy (CBT). Zolpidem is a rapid-acting, short-duration hypnotic that selectively binds to BDZ (ω) receptors containing α-1 subunits, which are associated with sedation. It is marketed in both immediate-release and extended-release formulations to decrease sleep latency. Due to its short-acting nature, zolpidem is administered immediately before bedtime in dosages of 5 or 10 mg.

Zolpidem is preferred for its selective activity, unlike BDZs, which non-selectively bind to all BZ receptor subtypes.[8] A meta-analysis evaluating the effectiveness and safety of zolpidem for the treatment of acute insomnia revealed that zolpidem increased the total sleep time of patients, reduced sleep latency, and increased sleep quality when compared with placebo.[9]

Purpose and scope of the expert opinion manuscript

Insomnia is often stigmatized due to societal prejudice. Patients are also known to internalize this stigma, which worsens the disorder and exacerbates the symptoms.[10] Furthermore, since patients with mental health disorders continue to be stigmatized and discriminated against in India, the data currently available on insomnia are sparse and unorganized.[11] Due to a lack of consensus, physicians across the country manage insomnia with varying treatment strategies, including the use of zolpidem.

Opinions were sought from several Indian experts to comprehensively understand the treatment landscape for insomnia in India and discuss the role of zolpidem in this context. Insights from expert opinions will help physicians understand the use of zolpidem in Indian patients with insomnia, the role of newer drugs in managing the condition, and implications for clinical practice and future research.

METHODS

The advisory board meeting was conducted in March 2023 in India with 33 eminent physicians representing various specialties, including internal medicine, psychiatry, neurology, diabetology, otorhinolaryngology, and cardiology. A total of three meetings, each consisting of 11 experts and steered by one moderator, were conducted. The key points of the discussions were summarized at the conclusion of the meetings by the moderator. Each meeting comprised three sessions focusing on the following topics—the current status of insomnia and related disorders in India, clinical experiences with zolpidem, and newer drugs for managing insomnia. The discussion guide for the advisory board meeting is outlined in Table 1.

Table 1: A discussion guide for the advisory board meeting.

S. no.	Questions
	Area 1: Insomnia: overview
1	How commonly do you see cases of insomnia in your clinical practice?
2	What, in your opinion, are the common reasons for insomnia in the Indian scenario?
3	Apart from insufficient sleep, are there any additional symptoms that your patients with insomnia complain of?
4	In which patient profiles do you find a higher prevalence of insomnia? Is insomnia linked to any personality trait as well?
5	How do you evaluate your patients for insomnia? Questions asked during history-taking, questionnaires used, and investigations
6	Do you do additional investigations to rule out any associated comorbidities (medical/psychiatric) or underlying causes for insomnia? Please elaborate.
7	How can insomnia disorders be differentiated from anxiety, depression, and panic disorders?
8	Which guidelines do you refer to for managing your patients with insomnia?
9	What is the level of awareness among Indians regarding chronic insomnia and its consequences for health?
	Area 2: Clinical experiences with the use of zolpidem in Indian patients
1	What are the factors that guide the choice of treatment for insomnia in your practice? Patient-related (age, associated comorbidities), disease-related (acute or chronic), and doctor-related
2	What are the limitations of the currently available treatment options for managing insomnia?
3	In which patient profiles do you recommend zolpidem? Why?
4	What is the duration for which you prescribe zolpidem to your patients?
5	What is the strength of choice for initiating the zolpidem treatment (5 mg/10 mg) in the following subgroups? Adults aged 18–55 years, women, and elderly (aged >55 years)

Continued.

S. no.	Questions
6	What are the advantages of zolpidem over other molecules (BDZs, melatonin, zolpidem + melatonin) in the treatment of insomnia and related sleep disorders?
7	Do you feel introducing additional formulations of zolpidem (e.g., oral dispersible, sustained-release, oral spray) will be beneficial for your patients?
8	How do you measure the response to therapy in your practice? What is the frequency of assessing the patient?
9	What are the limitations/drawbacks of zolpidem in managing insomnia in your practice?
10	What is the patient's feedback on treatment with zolpidem?
	Area 3: Newer drugs for managing insomnia
1	Have you used lemborexant in any of your patients with insomnia? What is the response to therapy? Preferred dose and duration of therapy, suitable patient profiles, efficacy, potential adverse effects, and current status in managing insomnia
2	Have you used melatonin in your clinical practice? Please share your experience regarding using melatonin in your patients with insomnia? Preferred dose and duration of therapy, suitable patient profiles, efficacy, potential adverse effects, and current status in managing insomnia
3	Which of these molecules can help provide you with additional options for managing your patients with insomnia/sleep disorders?
	Area 4: Future initiatives
1	What scientific activities can be undertaken to educate healthcare professionals about the treatment of sleep disorders?
2	Please list the activities that can be undertaken to educate people on the implications of insomnia for health and the need to treat it.
3	In which segments/areas related to sleep disorders and their treatment do you feel that evidence is currently lacking? Would you be interested in being a part of clinical studies?

BDZs: Benzodiazepines

KEY OPINION AND OUTCOMES OF THE PANEL DISCUSSION

Burden and diagnosis of insomnia

Insomnia is a significant public health concern that not only affects physical health but also a person's mental well-being and QoL. The global prevalence of insomnia varies widely, exhibiting heterogeneity across genders and geographical, social, and economic conditions. Studies suggest that insomnia has a prevalence ranging from 10% to 25% in the general population, with a significantly higher prevalence in females.[12,13] In India, insomnia often goes undiagnosed and untreated due to limited awareness, stigma, and healthcare access barriers. The exact incidences of insomnia in India are unknown and remain a challenge to discover,[14] although a longitudinal study revealed that 37% of adults (age ≥45 years) in India have insomnia.[7] A meta-analysis of 100 articles on sleep disorders among Indians reported a prevalence rate of 25.7% for insomnia, highlighting the significance of the condition. However, due to scattered data and a lack of harmonization, determining the precise incidence of insomnia in India remains challenging.[15] Factors such as advancing age, female gender, loneliness, illiteracy, malnutrition, physical inactivity, chronic comorbidities, and smoking have been identified as significant stressors for patients with insomnia. In addition, although a few studies have highlighted correlations between insomnia and factors such as unemployment, lower education rates, and racial minorities, all of which are associated with an increased incidence of insomnia, these correlations are not well understood and require further exploration.[16-18] According to the AASM guidelines, insomnia can be diagnosed by checking for predisposing factors (such as hyperarousal, increased sleep reactivity, or increased stress response), perpetuating factors (such as conditioned physical and mental arousal), learned negative sleep behaviors, and cognitive distortions. The history of insomnia can be evaluated through complaints of difficulty falling asleep, perpetuating factors such as conditioned physicality, sleep-wake schedule, nocturnal symptoms, and daytime sleepiness.[19] The experts' opinions on the burden, prevalence, and diagnosis of insomnia in India are collated in Table 2.

Associations between insomnia and comorbidities

Insomnia with hypertension and cardiovascular diseases

Chronic insomnia has been significantly associated with a two-fold increased risk of hypertension. Similarly, studies have reported a 68% increased risk of acute myocardial infarction and an 85% increased risk of stroke in patients with insomnia. Sleep disturbances can contribute to dysregulation of blood pressure control mechanisms, exacerbating existing hypertension or predisposing individuals to hypertension.[20]

Insomnia with type 2 diabetes mellitus (T2DM)

Insomnia is prevalent among individuals with T2DM and has been linked to poor glycemic control, insulin resistance, and an increased risk of diabetic complications.

A meta-analysis suggested that patients with insomnia were at a significantly higher risk of T2DM (risk ratio [RR]: 1.63, 95% confidence interval [CI]:1.37–1.94, p<0.0001).[21] A retrospective cohort study conducted on 81,233 patients with diabetes suggested that patients with insomnia are 28% more likely to develop T2DM compared with those without insomnia (hazard ratio [HR], 1.28; 95% CI, 1.24–1.33).[22] Multiple studies have outlined the association of diabetic neuropathy with sleep-related disorders. A study evaluating 20 patients with diabetic neuropathy revealed a significant increase in sleep apnea syndrome in those patients compared with that in patients without diabetic neuropathy and healthy controls (p<0.0001).[23] An observational, cross-sectional study evaluating 11 patients with diabetic neuropathy revealed a unidirectional relationship between diabetic neuropathy and insomnia (p=0.001) on the Pittsburgh Sleep Quality Index metric.[24]

Bidirectional relationship of insomnia with anxiety

Insomnia and anxiety often coexist and have a bidirectional relationship. Epidemiological studies suggest that around 50% of individuals with anxiety experience insomnia, which can trigger or worsen anxiety symptoms. Sleep disturbances in individuals with anxiety disorders may also impair daily functioning and perpetuate anxiety symptoms.[25]

Insomnia with chronic pain

Chronic pain conditions such as fibromyalgia, arthritis, and neuropathic pain are commonly associated with insomnia. Sleep disturbances can exacerbate pain perception and reduce pain tolerance, creating a vicious cycle of sleep–pain interaction.[26]

Insomnia in specific populations: postoperative patients, healthcare workers, IT/software professionals

Certain populations, such as postoperative patients, healthcare workers, and individuals in high-stress occupations, are particularly vulnerable to insomnia due to factors such as pain, shift work, and job-related stressors. Tailored approaches to insomnia management are needed to address the unique needs of these populations.[27-29] The experts' opinions on the burden and associations between insomnia and comorbidities, including mental health disorders are listed in Table 3.

Effects of sleep architecture disruption and its role in the management of insomnia

Sleep architecture refers to the cyclical patterns of sleep stages that individuals experience throughout the night. Stage 3, also known as slow-wave sleep (SWS) or deep sleep, is crucial for physical and mental restoration.[30] Disruptions in sleep architecture, such as those caused by insomnia, can have profound effects on overall health and well-being.[31] Short-term disruptions lead to deteriorated QoL in adults with insomnia, while long-term disruptions lead to comorbidities such as hypertension, T2DM, renal failure, respiratory diseases, immune disorders, and gastroesophageal reflux disease.

Impact of BDZs on sleep architecture

Human sleep comprises phases of nonrapid eye movement (NREM) and rapid eye movement (REM), forming a continuous cycle known as "sleep architecture." BDZs prolong stage 2 NREM sleep, reduce stages 3 and 4 of NREM sleep, and decrease the duration of REM sleep during nocturnal sleep. This influence affects the "deep sleep" of an individual, resulting in subsequent cognitive and respiratory depression, which usually leads to next-day somnolence, ultimately affecting QoL. These variations in sleep stages may also contribute to concentration deficits. Thus, BDZ prescriptions for insomnia may have long-term side effects.[32] The consequences of stage 3 sleep cycle disruption can impair memory consolidation, cognitive function, immune responses, and hormone regulation, increasing the risk of various health problems, including obesity, cardiovascular disease, and mental health disorders.[31]

Awareness and management of insomnia

In developing countries, sleep health is rarely considered on national public health agendas. In India, although factors such as caste or tribal status, religion, and socioeconomic background are known to play a major role in the awareness of insomnia, the disease burden is still unknown due to a lack of data.[7] Recommendations to promote sleep hygiene include circadian rhythm health awareness, centralized data collection to understand the burden of insomnia, and the implementation of common public health policies.[33] CBT, light therapy, and exercise are considered nonpharmacological treatment modalities for managing insomnia.[34] Medications with indications approved for insomnia treatment include BDZ receptor agonists, melatonin receptor agonists, selective histamine receptor antagonists, and dual orexin/hypocretin receptor antagonists.[35] The experts' opinions on the awareness of insomnia and its management in India are listed in Table 3.

Once considered first-line agents for the treatment of insomnia, BDZs are also administered for their anxiolytic activity. Patients with acute coronary syndrome (ACS) are reported to have twice the anxiety levels (mainly associated with a fear of pain or death) compared with those without ACS, and BDZs can rapidly relieve anxiety in those with ACS.[36] The use of BDZs in the management of ACS to mitigate sympathetic overactivity is well established in cardiology literature, with guidelines from organizations such as the American College of Cardiology supporting its short-term administration.[37] However, prolonged use of BDZs, particularly alprazolam, often leads to dependence despite its initial perception as a safe medication with low abuse potential. Alprazolam,

specifically, is known to induce addictive tendencies, especially in patients who continue its use for years.[38] The expert opinions on the management of insomnia in patients with cardiovascular diseases are collated in Table 4.

Role of zolpidem in the management of insomnia

Unlike BDZs, Z-class drugs, such as zolpidem, are short-acting hypnotics that have a selective impact on stage 2 sleep without impacting stage 3 and REM sleep. Zolpidem is regarded as a reasonable therapeutic option due to the lower occurrence of residual daytime sleepiness. Zolpidem, an imidazopyridine hypnotic, selectively binds to the α-one subunit of gamma amino butyric acid (GABA) receptors. Due to this mechanism of action, it does not interfere with stages 2 and 3 of the sleep cycle, which in turn, reduces the risk of drug dependence and improves sleep quality. Zolpidem is administered for 2–4 weeks and dose tapering is usually needed if a patient is on 10 mg of the drug. The dose is usually reduced to 5 mg before withdrawing the treatment.[8] When abruptly discontinued, zolpidem outperforms BDZs like triazolam. Statistically superior results in total sleep time and sleep efficiency were noted in those treated with zolpidem than in those treated with triazolam on the first withdrawal night. Moreover, wakefulness after sleep onset (WASO) decreased after zolpidem use but abruptly increased after triazolam use. These findings, along with polysomnography evaluations, suggest that even after long-term treatment, zolpidem does not induce rebound insomnia.[39,40]

Zolpidem primarily interacts with cytochrome P450 (CYP) inducers (rifampicin), CYP inhibitors (azoles, ritonavir, and erythromycin), histamine H2 receptor antagonists (cimetidine and ranitidine), antidepressants, antipsychotics, antagonists of BDZs, and drugs causing sedation.[41] Hence, zolpidem is a safer alternative for patients with renal, cardiac, and respiratory comorbidities. A randomized, placebo-controlled trial evaluated 15 patients with heart failure and showed higher total sleep time, along with an increase in stage 3 NREM sleep. This led to an improvement in sleep structure in patients with heart failure.[42]

Zolpidem is known to have selective benefits in patients with non-dipping hypertension. A randomized trial reported that zolpidem was significantly effective in converting non-dipper hypertensive patients to dipper hypertensives when compared with placebo.[43] A study evaluating the effects of zolpidem on patients in a vegetative state revealed that one hour after administering zolpidem, patients with brain injuries experienced an increased cerebral state index and reduced burst suppression, indicating improved brain activity. Additionally, cerebral perfusion was enhanced in patients with contrecoup contusion and space-occupying brain compression, which implied that zolpidem effectively restores brain function in patients in a vegetative state after brain injury, particularly those with injuries in nonbrain-stem areas, and the improvement in brain function is sudden rather than gradual.[44]

Overdoses of Z-class drugs can be managed faster (full recovery within six hours) than those of BDZs. Z-class drugs are quickly absorbed, which rarely warrants decontamination methods. Flumazenil, a competitive BDZ antagonist, can reverse the sedative effects of all three Z-drugs—zolpidem, zaleplon, and zopiclone. In cases of zolpidem poisoning or overdose, flumazenil may be necessary. Bolus doses usually suffice, eliminating the need for infusions, which simplifies zolpidem overdose management compared with that of BDZs.[45] Expert opinions on the role of zolpidem in the management of insomnia in India are collated in Table 4.

Role of zolpidem in patients with insomnia and anxiety

Generalized anxiety disorder is characterized by the presence of at least three of the following symptoms—restlessness, fatigability, difficulty concentrating, irritability, muscle tension, and sleep disturbances. Studies suggest that symptoms of anxiety disorders overlap with those of insomnia since patients are often reported to develop insomnia after being diagnosed with anxiety.[46] To arrest this progression and manage insomnia with anxiety, a personalized treatment approach incorporating zolpidem along with psychotherapy and/or anxiolytic medications may be beneficial. Close monitoring for adverse effects and treatment responses is essential for optimizing outcomes. A treatment algorithm has been developed where an overview of zolpidem usage in patients with anxiety, insomnia, or both is differentiated, along with a pathway to outline its clinical usage suitably.[47-53] This algorithm is outlined in Table 4.

Zolpidem in adjunction with CBT

Use of zolpidem alongside CBT for insomnia treatment

Combining zolpidem with CBT for insomnia management may enhance treatment outcomes by addressing both physiological and psychological aspects of insomnia. While zolpidem provides symptomatic relief, CBT focuses on modifying maladaptive sleep behaviors and beliefs, offering a comprehensive approach to insomnia management.

Considerations for the duration of zolpidem use in conjunction with CBT

The duration of zolpidem use in conjunction with CBT should be individualized based on treatment response, severity of insomnia, and patient preferences. Gradual tapering of zolpidem may be necessary once improvements in sleep quality and adherence to CBT techniques are achieved to minimize the risk of dependence and rebound insomnia. Expert opinions on the role of adjunct zolpidem in the management of insomnia in India are listed in Table 5.[54,55]

Comparative data of zolpidem and other drugs in the management of insomnia

Advantages of zolpidem over other medications

BDZs

Zolpidem and similar Z-class drugs are preferred over BDZs as they offer selective action with less risk of respiratory depression, physical dependence, and cognitive impairment. While both BDZs and Z-class drugs potentiate GABA activity, the latter selectively bind to the α-1 (hypnotic) subunit, unlike the nonselective binding of BDZs to multiple GABA receptors. The half-lives of short- and intermediate-acting BDZs range from six to 17 hours, which may cause daytime issues such as daytime sleepiness. For instance, lorazepam, alprazolam, and temazepam have half-lives of 10–20 hours, 6–12 hours, and 8–22 hours, respectively. In contrast, zolpidem's half-life of 2–3 hours prevents daytime sleepiness.[56] Apart from BDZs, melatonin receptor agonists and orexin receptor antagonists are the other commonly utilized pharmacological agents for the treatment of insomnia.

Melatonin and ramelteon

An MT1 and MT2 receptor agonist, melatonin is known to modify the time to induction of sleep. While melatonin is available as a 3-mg tablet formulation in India, the data are inadequate to support its utility as a hypnotic.[14] It is reported that the combination of zolpidem and melatonin is not advantageous in insomnia management. However, melatonin, when taken alone, has been associated with non-impairment of memory or performance, making it an ideal candidate in a work setting. Despite this, the drug needs to be administered cautiously as the sleep-promoting effects of melatonin are known to be delayed for several hours.[57] Ramelteon, a melatonin agonist, selectively binds to the melatonin receptors in the suprachiasmatic nucleus. A meta-analysis revealed that while prolonged-release melatonin showed small to medium effects on subjective and objective sleep measures, ramelteon demonstrated larger effects, especially in patients aged >55 years. Ramelteon exhibited significant improvements in total sleep time and sleep onset latency over four weeks, with sustained efficacy in long-term use. Overall, both melatonin and ramelteon were found to be effective for insomnia treatment, with ramelteon showing particularly promising results, especially in older individuals.[58]

Orexin receptor antagonists

Orexins are chemical agents that regulate the sleep–wake cycle by promoting the aroused state. Simultaneous neuronal firing in the wake-promoting areas (tuberomammillary nucleus, dorsal raphe, and locus coeruleus) and inhibition of the areas promoting sleep (ventrolateral preoptic nucleus and median preoptic nucleus) are known to contribute to insomnia. Orexin receptor antagonists offer a dual inhibition mechanism by inhibiting orexin-A and orexin-B neuropeptides, thereby inhibiting wakefulness and decreasing arousal.[8] Drugs such as suvorexant and lemborexant are novel and emerging therapies with improved safety profiles compared with traditional hypnotics like zolpidem. However, data on the long-term effects of these drugs are inadequate for physicians to prescribe them for insomnia. Suvorexant, at dosages of 10, 20, 40, and 80 mg, is reported to significantly inhibit arousal after sleep when compared with placebo.[59] A network meta-analysis comparing the efficacy of lemborexant with that of other insomnia treatments revealed that lemborexant fares better than other treatments, such as other dual orexin receptor agonists, BDZs, and Z-class drugs, on objective outcomes, such as total sleep time, latency to persistent sleep, and sleep efficiency, while ranking second only to suvorexant in wake after sleep onset outcomes.[60-62] Expert opinions on the role of using melatonin and lemborexant alone or in combination with zolpidem in the management of insomnia in India are collated in Table 5.

Table 2: Expert opinions on the burden, prevalence, and diagnosis of insomnia in India.

S. no.	Expert opinions
1	Insomnia is a disorder characterized by decreased sleep, difficulty falling asleep, midnight or early morning awakenings, and the inability to fall back asleep once awakened.
2	Common symptoms of insomnia include next-day irritation, difficulty concentrating, memory impairment, impaired functioning, and feelings of low energy or fatigue.
3	Acute insomnia is characterized by a duration of less than 3 months, while chronic insomnia persists for more than 3 months.
4	India exhibits a high prevalence of insomnia, ranging from 13% to 47%, with a dramatic increase observed in the last 3 years.
5	Various demographic groups, such as adolescents and young adults, approach psychiatrists and physicians with complaints of lack of sleep, disturbed sleep, increased fatigue, next-day somnolence, etc. Primary insomnia (without underlying disorders) is on the rise in the younger age group due to increased screen time.
6	Insomnia is linked to various occupational risks, with patient profiles ranging as wide as army personnel, truck or bus drivers, information technology and software professionals, and even doctors. Lifestyle habits, such as irregular work hours, the use of electronic devices before bedtime, social media addiction, stress, and improper sleep hygiene, contribute to insomnia. Underlying psychiatric disorders further exacerbate the condition.

Continued.

S. no.	Expert opinions
7	Insomnia is more common in the urban population, driven by factors such as hectic lifestyles, personal life issues, and prevalent smoking habits.
8	Often, patients presenting with excessive daytime sleepiness or feelings of loneliness may also complain of insomnia. Alternatively, when doctors inquire about sleep, patients may raise these complaints.
9	From a neurologist's point of view, insomnia can result from associated headaches, pain, or musculoskeletal issues. Women are more likely to develop insomnia, especially during premenstrual syndrome and menopause.
10	Psychiatrists usually treat patients with primary insomnia, whereas other medical specialties often manage insomnia comorbid with other conditions; primary insomnia is seldom encountered in general medical practice and is more frequently addressed by psychiatrists.
11	Advancing age is one of the risk factors for insomnia.
12	The subjectivity of sleep is noteworthy. Many times, sleep might be normal, but patients' expectations might not be met.
13	Insomnia can be diagnosed by the presentation of one or more of the following factors: increased sleep latency (inability to fall asleep in the first 30 minutes), impaired functioning, nighttime awakenings, excessive daytime sleepiness (also known as daytime somnolence), non-refreshing sleep (despite sleeping for 8–9 hours), difficulty concentrating, and memory impairment
14	The diagnosis of insomnia requires a detailed patient history, including an assessment of sleep quality, sleep latency, and early morning awakenings.
15	Patient history shall also be considered for associated disorders, such as excessive snoring and obstructive sleep apnea. The patient's spouse or family members play a vital role in communicating this history with the physician.
16	Insomnia severity scales, such as the Insomnia Severity Index and Egbert’s Scale, are used to evaluate patients and monitor their response to therapy.
17	Polysomnography (sleep study) is not routinely performed for patients presenting with insomnia symptoms in India. The study is only conducted for suspicion of obstructive sleep apnea, sleep-related seizures, movement disorders, and parasomnia.
18	Social stressors, such as changes in place or type of employment, residence, etc., can also affect patients' prognoses.

Table 3: Expert opinions on the associations between insomnia and comorbidities, including mental health disorders, awareness, and management in India.

S. no.	Expert opinions
	Comorbidities associated with insomnia
1	New-onset T2DM, diabetic neuropathy, poorly controlled hypertension, mental health disorders, disorders related to the urinary tract—nocturia, dysuria, infections, restless leg syndrome, which may or may not result from iron deficiency anemia, and obstructive sleep apnea
2	Insomnia is a risk factor for the progression of underlying conditions, such as cardiovascular diseases. It is reported that patients with ACS and heart failure may have stress-induced insomnia for a few days immediately after the episode.
3	Associated comorbidities should be ruled out at the time of the diagnosis of insomnia. The underlying causes of comorbidities should be treated. For example, nocturia can be treated with better control of hyperglycemia, and restless leg syndrome can be treated with gabapentin or carbamazepine.
4	The reason for the early development of insomnia in patients with diabetes is unknown.
5	Social factors, such as high income or working in a service industry, are associated with insomnia.
	Association of mental health disorders with insomnia
1	Early-morning insomnia can be interpreted as a sign of depression. Patients with anxiety, avoidance personality traits, bipolar disorder, and an inclination toward perfection or OCD are at a higher risk for insomnia. It is noted that patients with mania have a lesser need for sleep.
2	Common causes of secondary insomnia include pain, underlying psychiatric illness (anxiety/depression, PTSD), neurological conditions like Parkinsonism and Alzheimer disease, hyperthyroidism, gastroesophageal reflux disease, substance abuse disorders, restless leg syndrome, etc.
3	Parasomnias are conditions that mimic insomnia but are primarily caused by conditions such as restless leg syndrome.
4	Initiatives to raise awareness about insomnia, its consequences, and available management options are crucial.
5	Simple questionnaires in local languages can help increase awareness among patients.

Continued.

S. no.	Expert opinions
6	Many individuals perceive insomnia as a normal part of life, unaware that it is a disorder, which leads them to avoid seeking help.
7	Sometimes, patients may mention the disorder casually to the treating physician or family doctor, who may not take it seriously.
8	Awareness about the long-term consequences of insomnia on general health is lacking not only among patients but also among healthcare professionals in India.
9	Non-pharmacologic interventions to manage insomnia include sleep hygiene education along with relaxation techniques such as yoga nidra and symptomatic relaxation exercises.
10	BDZs are prescribed for patients with insomnia who are experiencing symptoms of anxiety. However, withdrawing drugs such as BDZs, TCAs, or other GABAergic medications can result in rebound insomnia.
11	Alcohol consumption is known to alter sleep architecture.

ACS: Acute coronary syndrome; BDZ: benzodiazepine; GABA: gamma-aminobutyric acid; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; TCA: tricyclic antidepressant; T2DM: type 2 diabetes mellitus

Table 4: Expert opinions on the management of insomnia in patients with cardiovascular diseases and the role of zolpidem in the management of insomnia.

S. no.	Expert opinions
	Management of insomnia in patients with cardiovascular diseases
1	Cardiologists usually administer BDZs for a short time after managing ACS to reduce sympathetic overactivity.
2	However, patients tend to continue using alprazolam for longer than the recommended period (up to several years) and develop a dependence on the drug. In such patients, it is difficult to taper and stop BDZs.
3	Despite the perception of alprazolam as a safe drug with low abuse potential, it is one of the most abused medications, along with proton pump inhibitors.
4	Alprazolam presents a high risk of addiction and dependence, as evidenced by symptoms such as akathisia or restlessness, where patients find it difficult to remain still or relax.
5	An ideal approach would be to recommend BDZs for a short time after ACS (5–7 days) and then switch to zolpidem for ~4 weeks to enable patients to sleep better.
6	Among BDZs, etizolam has a shorter half-life and, hence, should be preferred.
	Role of zolpidem in the management of insomnia
1	Zolpidem is recommended by physicians across specialties for its efficacy, safety profile, and minimal impact on sleep architecture.
2	Zolpidem is preferred as a first-line pharmacotherapy for insomnia, even in patients with renal, cardiac, and respiratory comorbidities, and can be safely used in various populations, including the elderly.
3	Zolpidem is preferred for the following reasons: it has a well-researched profile, which includes expansive data; it exhibits selective GABA-A action, which does not impair stage 3 sleep, which is essentially restorative sleep; its non-addictive nature leaves no next-day somnolence. Zolpidem, with its short half-life, allows for abrupt discontinuation without the need for tapering. This cessation does not induce dependence or trigger rebound insomnia or withdrawal symptoms. However, it is advisable for patients on 10 mg zolpidem to initially taper to 5 mg over 1–2 weeks before complete cessation.
4	Treatment duration typically spans 2–4 weeks.
5	For the elderly population, a lower dose (5 mg) is recommended. Zolpidem abuse is uncommon but has been observed in elderly patients.
6	Zolpidem has shown efficacy in improving sleep continuity and quality without significant adverse effects.
7	Zolpidem has minimal drug–drug interactions with drugs used to treat hypertension or T2DM. Additionally, it does not cause respiratory depression or have any muscle relaxant properties, which is beneficial in patients with congestive cardiac failure and insomnia.
8	Non-dipping hypertensive patients with insomnia might become normotensive at night with zolpidem therapy.
9	Recent studies have demonstrated that zolpidem has a beneficial effect on patients in a vegetative state or coma, helping facilitate neuronal recovery.
10	Zolpidem demonstrates a relatively lower risk of adverse outcomes in cases of overdose compared with other hypnotic agents. Administration of flumazenil has been effective in reversing its effects, leading to complete recovery in patients.
	Algorithm for the treatment of patients with anxiety, insomnia, or both
	Initial assessment
	Gather patient history, including sleep patterns, chief complaints, anxiety symptoms, medical history, and current medications. Perform a physical examination to rule out any underlying medical conditions contributing to the symptoms.

Continued.

S. no.	Expert opinions
	Differential diagnosis
	Anxiety disorders: characterized by excessive worry, restlessness, irritability, muscle tension, and difficulty concentrating; insomnia disorders: characterized by difficulty initiating or maintaining sleep, waking up too early, or non-restorative sleep; and combined anxiety and insomnia: presence of symptoms from both anxiety and insomnia disorders.
	Diagnostic evaluation
	Validated screening tools, such as the GAD-7 scale and the ISI, should be used to assess symptom severity. Additional assessments like sleep diaries and actigraphy should be considered to quantify sleep patterns objectively.
	Treatment planning
	Treatment should be customized based on the predominant symptoms and severity. Non-pharmacological interventions: CBT for insomnia management, CBT for anxiety management, relaxation techniques, stress management, and sleep hygiene education. Pharmacological interventions - for insomnia: zolpidem (a non-BDZ hypnotic) can be prescribed at night for sleep initiation, start with the lowest effective dose; for anxiety: BDZs can be prescribed during the day for anxiety management, start with the lowest possible dose and use it for short-term relief; and combined therapy: consider combining pharmacological and non-pharmacological interventions for comprehensive management.
	Monitoring and follow-up
	Regularly monitor treatment response, side effects, and adherence. Adjust treatment as needed based on the patient's progress and preferences. Encourage lifestyle modifications and ongoing psychological support.
	Referral
	Consider referral to a psychiatrist or sleep specialist for complex cases or when initial treatments are ineffective. Collaborate with other healthcare professionals to address comorbidities and optimize patient care.
	Education and support
	Provide education about the nature of anxiety and insomnia disorders, treatment options, and the importance of adherence to therapy. Offer support and encouragement throughout the treatment process.

ACS: Acute coronary syndrome; BDZ: benzodiazepine; CBT: cognitive behavioral therapy; GABA: gamma-aminobutyric acid; GAD-7: generalized anxiety disorder 7-item; ISI: insomnia severity index; T2DM: type 2 diabetes mellitus.

Table 5: Expert opinions on the current management and future directives for the management of insomnia in India.

S. no.	Expert opinions
	The management of insomnia using adjunct zolpidem
1	Pharmacotherapy, particularly zolpidem, is the mainstay for insomnia treatment in India, often accompanied by CBT or lifestyle modifications.
2	CBT is not routinely advised, as patients often prefer pharmacotherapy as a first-line treatment due to their desire for quick relief.
3	Zolpidem usage can be discontinued after 3–4 weeks once the effects of sleep hygiene measures or CBT become evident.
4	Patient counseling should include advice on avoiding central nervous system stimulants, such as caffeine, and reducing screen time.
	The use of melatonin and lemborexant alone or in combination with zolpidem in the management of insomnia
1	Melatonin is preferred in the management of sleep–wake cycle disturbances and in patients with jetlag, as it has free radical scavenging and immune-stimulating properties. However, melatonin's efficacy is limited. It is not a sedative, but it helps keep patients relaxed. Improved efficacy of melatonin is observed with decreased exposure to light.
2	Melatonin primarily serves as an adjunctive therapy, with limited efficacy as a standalone treatment.
3	The combination of zolpidem and melatonin is utilized in specific conditions, such as in patients with neuropsychiatric disorders.
4	Long-term data on the safety and efficacy of melatonin are lacking. Furthermore, evidence suggests that melatonin might increase glycemic levels and blood pressure, rendering it unsuitable for patients with T2DM and hypertension.
5	Lemborexant, a novel dual-orexin receptor antagonist, offers potential benefits but is expensive and has a long half-life, leading to excessive daytime sedation.

Continued.

S. no.	Expert opinions
6	Healthcare providers have limited experience with lemborexant, and there are gaps in the data regarding its long-term use and safety.
7	Side effects of lemborexant include headaches and an increased risk of falls and fractures in elderly patients, along with reduced ability to perform routine activities and decreased sleep satisfaction.
8	While the combination of zolpidem with other agents like melatonin or lemborexant is being explored, the evidence supporting such combinations is limited. The zolpidem–melatonin combination does not offer added advantages or efficacy over zolpidem alone. Since current clinical evidence has failed to demonstrate the tangible benefits of this combination, it is advisable to avoid the combination.
9	Alternative treatments like melatonin or ramelteon are less preferred over zolpidem due to concerns regarding their efficacy.
	Indian Society for Sleep Research recommended nonpharmacological treatment modalities
1	Sleep hygiene education: Maintain sleep times, exercise, avoid inactivity, avoid consuming anything 3 hours before bedtime, and ensure comfort and quietness in the bedroom.
2	Relaxation therapy: Progressive muscle relaxation, biofeedback techniques, deep breathing, autogenic training, body scanning, abdominal breathing, hypnosis, and meditation.
3	Cognitive therapy: Aims at reducing the excessive tracking of the daytime consequences of insomnia.
4	Sleep restriction therapy: This involves restricting the amount of time spent in bed to nearly match the actual amount of sleep being achieved; following this, the time spent in bed can be gradually increased as sleep efficiency improves.
5	Stimulus control therapy: This recommends sleeping only when tired, using the bedroom only for sleeping, waking up at a similar time every day, and avoiding napping during the day.
6	Cognitive behavioral therapy for insomnia: Stimulus control, sleep restriction, and relaxation training.
7	Brief behavioral treatment for insomnia: Delivered over 4 consecutive weeks (as four sessions; one every week); it focuses on altering behaviors to improve sleep.
8	Miscellaneous interventions: Mindfulness, hypnotherapy, paradoxical intention, intensive sleep retraining, bright light therapy, and yoga nidra.
	Indian Society for Sleep Research recommended pharmacological treatment modalities
1	BDZs: Lorazepam, flurazepam, brotizolam, lormetazepam, temazepam, and triazolam
2	Z-class drugs: Zolpidem, zaleplon, zopiclone, and eszopiclone
3	Melatonin-receptor agonists: Ramelteon
4	Dual-orexin receptor antagonists: Suvorexant, almorexant, lemborexant, and filorexant
5	Antidepressants: Rarely recommended (low evidence)
6	Antipsychotics: Chlorprothixene, levomepromazine, olanzapine, pipamperone, prothipendyl, and quetiapine; mostly used as off-label treatments
7	Miscellaneous: Antihistamines, phytotherapeutics, anticonvulsants
	Future directives for the management of insomnia in India
1	Launching initiatives to raise awareness about insomnia, its consequences, and available management options is imperative. This should include distributing educational materials on sleep hygiene.
2	The development of educational materials and screening tools, including self-assessment tools, is necessary for both healthcare professionals and the general population.
3	Key opinion leaders should collaborate to establish standardized management protocols and conduct training programs for healthcare professionals. Furthermore, initiatives like speaker programs and train-the-trainer programs should be implemented to enhance awareness among physicians on insomnia management approaches and the role of medications like zolpidem.
4	Continuous education programs are essential for improving healthcare professionals' understanding of the role of pharmacotherapy in managing insomnia.
5	Establishing an insomnia disease registry specifically for India can yield valuable insights into the prevalence and characteristics of insomnia in the Indian population, facilitating the collection of actual data on its incidence and prevalence.
6	Research efforts should prioritize evaluating newer therapies, assessing long-term outcomes, and addressing knowledge gaps in insomnia management.
7	Encouraging individuals to complete sleep score questionnaires and raising awareness about the health-related consequences of chronic insomnia are crucial steps in promoting better sleep quality.

BDZ: Benzodiazepine; CBT: cognitive behavioral therapy; T2DM: type 2 diabetes mellitus

Indian guidelines on the treatment of insomnia and international recommendations from key guidelines

A comprehensive consensus statement by a joint venture from the Association of Physicians of India and the Indian Society for Sleep Research (ISSR) in 2022 outlined the definitions, epidemiology, risk factors, presentations, evaluation, diagnosis, and management of insomnia in India. The statement was based on a comprehensive search and review of relevant literature published until 2022 on patients with insomnia aged >18 years.[14]

While treating insomnia, the primary outcomes of interest are sleep quality improvement, efficiency in daytime functionality, and prevention of relapse. To achieve these outcomes, the management of insomnia is categorized into nonpharmacological and pharmacological treatments. While deciding on the treatment modality, individual factors such as severity, impact, urgency of resolution, cost, preferences, accessibility, and side effects need to be considered. Non-pharmacological modalities include behavioral or cognitive measures. While pharmacological modalities offer quick relief from the symptoms of insomnia, it is always recommended that comorbid insomnia be treated along with the underlying cause. Pharmacological therapies are often short-term treatments for insomnia and need to be considered based on patient-specific circumstances. Both the ISSR and AASM recommend Z-class drugs for short-term use. While BDZs are efficacious in inhibiting GABA receptors, they are not preferred as first-line pharmacotherapeutics in the initial and maintenance therapy for insomnia.[14] A short brief on the management of insomnia with the future directives for the management of insomnia in India are outlined in Table 5.[14]

Figure 1: QR code for the Indian insomnia sleep score questionnaire.

Questionnaires such as the Pittsburgh sleep quality index, oviedo sleep questionnaire, Athens insomnia scale (AIS), and insomnia severity index aid in both the diagnosis of insomnia and reassessments after treatment. However, sleep patterns vary across cultures, which makes the utilization of a single questionnaire challenging for the global population. A validated questionnaire based on the AIS to grade the severity of insomnia in the Indian population, known as the Indian insomnia sleep score (IISS), is now available.[63] Indians, in general, lack awareness of insomnia or sleep-related disorders. The questionnaire was validated with excellent Cronbach's α values of >0.9, a high level of homogeneity, 100% sensitivity, and 90% specificity. The questionnaire can be accessed at https://www.lybrate.com/abzo2.[63] The QR code for the IISS questionnaire is provided in Figure 1.

CONCLUSION

This expert opinion manuscript provides valuable insights into the management of insomnia and related disorders. Prolonged use of BDZs, particularly alprazolam, often leads to dependence and addiction, and patients continue to use it for years. Zolpidem is currently the preferred first-line pharmacotherapy for the treatment of insomnia as it does not alter sleep architecture, prevents daytime sleepiness, has a non-addictive nature, and its abrupt discontinuation does not induce dependence, withdrawal symptoms or trigger rebound insomnia; it is, therefore, recommended by Indian and American guidelines. Although zolpidem provides effective treatment when compared with BDZs and other drugs, caution should be exercised while prescribing zolpidem. Nonpharmacological interventions, such as maintenance of sleep hygiene measures and CBT, are deemed essential in the management of insomnia. Future directives stress the importance of standardized management protocols, continuous education, and research efforts to address knowledge gaps and improve outcomes in insomnia management in India.

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