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Selecting a pharmacotherapy regimen for patients with chronic insomnia

Amanda B. Hassinger[a,b], **Nikolas Bletnisky**[a,b], **Rizwan Dudekula**[a,b], **Ali A. El-Solh**[a,b,c]

[a]Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY, USA;

[b]VA Western New York Healthcare System, Buffalo, NY, USA;

[c]Department of Epidemiology and Environmental Health, Research and Development, School of Public Health, University at Buffalo, Buffalo, NY, USA

Abstract

Introduction: Chronic insomnia, whether it is primary or in combination with another medical or psychiatric disorder, is a prevalent condition associated with significant morbidity, reduced productivity, increased risk of accidents, and poor quality of life. Pharmacologic and behavioral treatments have equivalent efficacy with each having its own advantages and limitations.

Areas covered: The purpose of this perspective is to delineate the limitations encountered in implementing cognitive behavioral therapy (CBT) and to review the pharmacological treatments designed to target the different phenotypes of insomnia. The discussions address how to choose the optimal medication or combination thereof based on patients' characteristics, available medications, and the presence of comorbid conditions. Selective nonbenzodiazepine sedative 'Z-drug' hypnotics, melatonin receptor agonist-ramelteon, and low-dose doxepin are the agents of choice for treatment of primary and comorbid insomnia.

Expert opinion: A pharmacological intervention should be offered if cognitive behavioral therapy for insomnia is not available or has failed to achieve its goals. Increasing evidence of the significant adverse consequences of long-term benzodiazepines should limit the prescription of these agents to specific conditions. Testing novel dosing regimens with a combination of hypnotic classes augmented with CBT deserve further investigation.

Keywords

Pharmacotherapy; cognitive behavioral therapy; hypnotics; antidepressants; off-label

CONTACT Ali A. El-Solh, solh@buffalo.edu, VA Western New York Healthcare System, Research Building - 203495 Bailey Avenue, Buffalo, NY 14215, USA.

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1. Introduction

Insomnia is one of the most prevalent sleep disorders worldwide [1]. It is the second most common psychological health problem, affecting one in three adults in the United States [2] and 10% to 15% of people worldwide [1,3,4]. According to WHO data, insomnia ranked 11th in the list of most important brain disorders with respect to global burden [5]. Insomnia has been consistently associated with problems with cognitive function, impaired mental health and poor health-related quality of life [6–8]. In addition to accounting for 5 million doctor visits annually [9], untreated insomnia is financially costly in its associated loss of work-place productivity, increased absenteeism, and work-related accidents [8,10]. Conservative estimates of the total direct cost to the US economy ranges between 1 USD.9 billion to 92 USD.5 billion annually [11,12].

The two widely practiced treatment modalities for insomnia are cognitive behavioral therapy (CBT) and pharmacotherapy [13]. Although hypnotic medications are indicated in situational insomnia, psychological and behavioral factors are almost always an integral component of persistent insomnia. Addressing these behavioral aspects should be the first step toward a satisfactory response. Prior meta-analyses [14,15] have shown that CBT is an efficacious treatment for reducing sleep latency, wake time after sleep onset, and early morning awakenings, as well as increasing sleep efficiency. Further, these studies have demonstrated that CBT performs as well as pharmacotherapy or even slightly better in the short term [16], with superior results in the long term [17]. CBT has many advantages over hypnotics including fewer side effects, more cost-effective, and safer to use during pregnancy and breastfeeding [18]. Realistically, however, only a third of patients with insomnia experience full remission and a significant proportion experience residual sleepiness following CBT. Faced with these scenarios, a variety of pharmacological agents are used by physicians to treat this disorder, including those agents approved by the Food and Drug Administration (FDA) for insomnia, as well as medications that have sedating properties, but have not been systematically studied for their effectiveness in randomized controlled trials. The specificity and the chronicity of the patient’s sleep complaint as well as the presence of concomitant medical and/or psychiatric comorbid conditions should guide the prescribing provider in choosing the appropriate hypnotic agent.

This review is intended to lay out the rationale behind prescribing hypnotics for insomnia and to provide guidance on drug selection. We will also identify opportunities for future research to further this important area of medicine.

2. Cognitive behavioral therapy limitations

CBT is a non-pharmacologic intervention designed to modify learned-behavioral maladaptation to aberrant sleep patterns. While a detailed analysis of its efficacy and effectiveness is beyond the scope of this review, there are instances when CBT may not be a robust enough treatment to reduce symptoms of insomnia or practical enough to be applied universally. The two major barriers to more widespread use of CBT are the lack of CBT expertise and the limited awareness of its efficacy. Despite the strong recommendations adopted by sleep societies for CBT in treating insomnia [19,20], not all sleep clinics offer

CBT. In the interest of increasing access and reducing cost, many groups have developed simplified or abbreviated versions of CBT for insomnia, organized training programs for advanced master's level providers including nurse practitioners and physician assistants, and/or using technology, such as Interned-based programs [21–23]. Nonetheless, between 19% and 26% of insomnia patients fail to show any response to CBT-I and the effect size of CBT in insomnia is far less than that of CBT for anxiety, post-traumatic stress disorder (PTSD), depression, or panic disorder [14]. Given the inherent selection bias in study populations consenting to enroll in CBT research, real-life CBT completion rates could be well over-estimated. In addition, CBT drop-out rates range from 22% to 30% [24]. Even when patient motivation is intact, aspects of CBT can lend patients to drop-out. Among the features cited for CBT nonadherence are the reported social isolation derived from lack of flexibility, boredom from imposed wakefulness during-re-entrainment, and rigidity of the sleep schedule often incompatible with working hours.

Several patient-specific contexts make aspects of CBT challenging and ineffective. CBT efficacy is largely dependent on the patients' commitment and self-efficacy [17]. Insomnia patients who perceive CBT treatment as 'annoying' or 'boring' derive poorer treatment outcomes [25]. Overall, patients who endorse biological causes prefer pharmacotherapy and those who endorse psychosocial causes prefer psychotherapy [26]. Hence, patient preference should be taken into consideration when a plan of treatment is formulated.

More recently, two distinct phenotypes of insomnia on the basis of objective total sleep time have been described that differ in etiology, pathophysiology, biological severity, natural course, psychological characteristics, and, their specific treatment needs [27]. The first phenotype with sleep duration of less than 6 h is primarily associated with biologic vulnerability (genetic predisposition), physiologic hyperarousal, and impaired neurocognitive functioning, usually coinciding with significant medical comorbidities. The second phenotype defined as total sleep duration equal or exceeding 6 h is characterized by 'normative cognitive-emotional' and cortical arousal, associated with sleep misperception, 'anxious-ruminative traits,' and poor coping resource [28]. These two phenotypes differ in their response to treatment. It has been shown that the short sleep duration group was generally less responsive to CBT than was the normal sleep duration group. As such, it has been advocated that biologically based treatments that aim to reduce physiologic arousal, such as hypnotic medications may be more appropriate in patients with short total sleep time while individuals with the insomnia phenotype associated with regular sleep duration and normal cognitive arousal might be better served with a behaviorally based approach [29]. However, a recent study has casted doubt on this theory by showing that patients with reported short total sleep time had a beneficial response to CBT of greater magnitude than patients with normal sleep duration, although the patients with the shortest sleep phenotype experienced significant residual insomnia symptoms after treatment [30].

3. Approach to selecting appropriate pharmacologic treatment for insomnia

The goals of treatment for insomnia are to bring around the misaligned homeostatic and circadian drives which have resulted in the underlying sleep disturbance. The choice of pharmacotherapy will depend on the specific insomnia symptoms, their severity and duration, the drug efficacy and safety, as well as co-morbid disorders. Indications and dosage of sedative hypnotics are provided in Table 1. In contrast to patients presenting with an acute onset insomnia of short duration where the use of a FDA-approved hypnotic for several consecutive nights is usually sufficient for patients to overcome the stressful event, in chronic insomnia, it is recommended that patients receive appropriate treatment for co-existing medical and psychiatric disorders that contribute to the sleeping disorder (i.e. depression, pain, dyspnea, nightmares, restless leg syndrome) prior to instituting insomnia medications [31]. Once the decision is made to institute pharmacotherapy, it is desirable to select a hypnotic agent that displays rapid onset of action, optimal duration of action, and preservation of sleep architecture, while at the same time is devoid of morning residual sleepiness and/or memory loss, and does not interact additively or synergistically with other medicines to produce untoward side effects. There is a general consensus that pharmacotherapy should be initiated at the lowest effective dose and for a short-term duration, i.e., 4 weeks or less. However, in reality, this short duration may not be effective or acceptable to patients. Longer course of treatment may be warranted for those who demonstrate sustained response in the absence of adverse events and have a regular follow-up visit with their health-care providers.

3.1. Primary insomnia

Traditionally, primary insomnia has been classified into three subtypes: sleep-onset insomnia, sleep-maintenance insomnia, or insomnia associated early morning awakening. However, this categorization should be viewed as a dynamic rather than a static representation of sleep condition. It is not unusual that sleep-onset insomnia evolves with time into sleep-maintenance insomnia or to converts into both sleep onset and sleep-maintenance insomnia [32]. Hence, once pharmacotherapy is initiated, follow-up and re-assessment should be conducted on a regular basis to ensure that the subtype of insomnia has not progressed to another insomnia phenotype or that new comorbidities did not emerge.

Considering the multitude of FDA-approved hypnotics, the non-benzodiazepine benzodiazepine receptor agonists, zolpidem, and zaleplon are considered the agents of choice in facilitating sleep onset [33]. Both of these agents have a relatively short half-life with rapid onset of action. Zolpidem is less disruptive of sleep stages and has lesser effects on next-day psychomotor performance compared to other benzodiazepine hypnotics [34]. Additionally, rebound insomnia and other withdrawal effects have not been demonstrated with zaleplon [35]. Newer zolpidem modifications have provided alternative delivery systems in order to increase the drug’s efficacy and target specific sleep disturbances. Two sublingual oral formulations-zolpidem SL (Edluar and Intermezzo) and an oral spray (Zolpimist) are available. While the sublingual tablets Edluar and the oral spray preparation are marketed for sleep-onset insomnia, the other sublingual formulation (Intermezzo) is

indicated for middle-of-the-night-wakefulness with difficulty returning to sleep. Alternatively, ramelteon, a melatonin receptor agonist, approved for the treatment of sleep-onset insomnia, is one of two hypnotics that are not schedule-controlled drugs by the Drug Enforcement Agency (DEA). Its mechanism of action involves promoting drowsiness via MT1 receptor stimulation and synchronizing the circadian clock via MT2 receptor [36]. Because benzodiazepine-GABA-A receptors are not engaged, ramelteon is considered free of possible drug abuse, dependence, and next-day cognitive dysfunction although anecdotal evidence may suggest otherwise [37]. It has been proven also to reduce sleep latency in geriatric patients without impairing mobility or memory functions [38]. In 2010, the FDA approved doxepin (Silenor, 3 and 6 mg) for sleep-maintenance insomnia. In contrast to the high doses used to treat depression (75 to 300 mg), low doses of doxepin have been shown to exhibit highly selective H_1 antagonism [39]. In clinical trials, doxepin was found to be effective for maintenance sleep problems with minimal associated next-day residual effects [40]. In addition, it does not have any associated complications of abuse, tolerance, withdrawal, or complex sleep behavior. However, it should be avoided in the presence of untreated narrow angle glaucoma or severe urinary retention because of its anticholinergic effects though these are minimal at the doses used for insomnia. Similar to ramelteon, doxepin is not a DEA scheduled hypnotic.

For patients who are experiencing both sleep-onset and sleep-maintenance insomnia, the choices are more diverse. The treatment selection can consist of a single agent or a combination of agents with the different onset of action. Eszopiclone is particularly well suited for this insomnia phenotype given its long half-life [41]. Higher doses (2 to 3 mg) are more effective for sleep maintenance, whereas lower doses (1 to 2 mg) are suitable for difficulty in falling asleep. Eszopiclone is among the few hypnotics that have been studied in double-blind, placebo-controlled, randomized trials of nightly administration for a period of 6 months [42] and is approved for the long-term treatment of sleep-onset and sleep-maintenance insomnia. One common adverse effect of eszopiclone is an unpleasant taste that affects nearly one-third of patients at the maximum recommended dosage [41]. Other agents that may be considered for chronic insomnia include zaleplon for sleep-onset insomnia and zolpidem CR for both sleep onset and sleep-maintenance insomnia. Both long-term trials of zaleplon and controlled-release (CR) zolpidem have shown a sustained response with no tolerance and dependence after 6 months of daily use [43,44]. The sedating profile of Zolpidem CR (6.25 and 12.5 mg dose) is attributed to its unique composite preparation which has a component that releases immediately and a component that is slowly released, allowing higher blood levels later in the sleep cycle. Notwithstanding the favorable safety profile of non-benzodiazepines compared to traditional benzodiazepines, a series of case reports have raised concerns about complex sleep-related behaviors (e.g. sleep walking, sleep driving) that have been linked to serious bodily injuries [45]. In response, the FDA has issued a black box warning recommending to avoid using these agents in patients who have previously experienced similar nocturnal episodes [46].

A representative of a new class of hypnotics, the orexin receptor antagonists, suvorexant, has been approved by the FDA in August 2014 for the treatment of primary insomnia of the sleep-onset and sleep-maintenance subtypes. However, suvorexant increases nocturnal sleep mainly by reducing wake after sleep onset (WASO) [47,48]. Suvorexant effect on sleep

onset is substantially weaker compared to other short-acting hypnotics like zaleplon or triazolam. Despite the limited safety data on its prolonged use, our approach still favors the use of this agent for coexisting sleep onset and sleep-maintenance insomnia because difficulty staying asleep is more common than difficulty falling asleep particularly for patients over the age of 40 [49]. The current recommended dose is 10 mg to 20 mg daily. Like most hypnotics, suvorexant can be responsible for daytime sleepiness, fatigue, narcolepsy-like symptoms, and in rare instances suicidal ideation [49]. Lemborexant is the most recent drug in the orexin receptor antagonists class to receive approval from the FDA for the treatment of sleep onset and or sleep-maintenance insomnia [50]. Its mechanism of action parallels that of suvorexant. Similar to nonbenzodiazepine benzodiazepine-receptor agonists, both suvorexant and lemborexant are a schedule IV controlled substance.

Combining two medications to address symptoms of both sleep-onset and sleep-maintenance difficulties is uncommon and discouraged. Problems with adherence and drug-drug interactions become of significant concern when such a regiment is prescribed. Nonetheless, doxepin in combination with zaleplon, zolpidem, or ramelteon may be offered when monotherapy has failed to achieve the desired outcomes or has resulted in adverse reactions.

Sedating antidepressants (e.g., amitriptyline, trazodone, mirtazapine) are often prescribed off-label as sleeping aids [51] despite the fact that randomized clinical trials addressing the efficacy and safety of these agents in primary insomnia are lacking. Similarly, the use of atypical antipsychotics (quetiapine, olanzapine) in primary insomnia lacks well-defined studies to support their efficacy. There is a general consensus that these agents should not be prescribed even when used at low doses [52]. Besides, these agents carry serious side effects including weight gain, tardive dyskinesia, and diabetes.

3.2. Comorbid insomnia

Comorbid insomnia has an intricate interplay with mental health and other disease processes that make it distinct from primary insomnia in both diagnosis and management. As with primary insomnia, patients with comorbid insomnia may experience sleep-onset insomnia, sleep-maintenance insomnia, or early-morning awakenings coupled with an inability to return to sleep. However, frequent night awakenings are particularly common in patients with comorbid conditions with more than 90% of subjects reported awakening at least one time every night for more than 6 months [53]. Treatment of comorbidities such as pain, fatigue, depression, anxiety, or dyspnea or identification of medications (e.g., corticosteroids, SSRI) that can disrupt sleep architecture and exacerbate sleep issues is a critical first step in the management of sleep disturbances in these patients [54]. However, addressing the underlying medical or psychiatric condition may not always translate into the complete resolution of insomnia [55,56].

When pharmacotherapy is used, the consensus is to select agents targeting both sleep problems and comorbid conditions. To that end, the selection of a specific treatment for insomnia is dictated usually by the clinical situation. For example, review of the literature offers four distinct approaches regarding the clinical management of insomnia in the setting of depressive disorders: 1) initiating an antidepressant therapy with intrinsic sleep-promoting

properties (mirtazapine, trazodone, or a sedating tricyclic antidepressant); 2) initiating a selective serotonin reuptake inhibitors (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI), in combination with a sleep promoting hypnotic; 3) initiating SSRI without additional treatment for insomnia anticipating abatement of symptoms when depression subsides; and 4) combining an antidepressant (SSRI or SNRI) with CBT. It is important to keep in mind that some antidepressant medications, such as SSRI or SNRI can worsen insomnia necessitating a concomitant sleeping aid. For example, eszopiclone when added to fluoxetine not only can improve insomnia but also increase the efficacy and response rate of the antidepressant response to fluoxetine [57]. A similar outcome was observed when zolpidem was used with escitalopram [58].

Although sedative antidepressants (e.g., trazodone, amitriptyline, mirtazapine) have been used in patients with depression complicated by insomnia, double-blind placebo-controlled studies to document the effectiveness of these drugs have not been undertaken. Further, the hypnotic properties of antidepressants such as trazodone or doxepin has been described at 'low' doses. Using these agents at doses required to control depression (threefold higher for trazodone and nine fold higher for doxepin) may not hold the same efficacy for managing concomitant insomnia. Given that there is no clear consensus in regard to the dose range for the hypnotic efficacy and safety of these drugs, it is recommended that these agents not be used as first-line agents.

Post-traumatic stress disorder is another challenging comorbidity where insomnia is a prominent feature [59]. In general, insomnia and nightmares account for the majority of the sleep disturbances observed in patients with posttraumatic stress disorder [60]. Although CBT remains the preferred treatment modality for insomnia, 50% of PTSD patients continue to report residual insomnia despite no longer meeting criteria for PTSD [61]. In response, benzodiazepines have been widely used to diminish anxiety-related PTSD and facilitate sleep. However, recent data have demonstrated that BZDs are associated in worse overall PTSD outcomes when compared with placebo [62,63]. The use of these hypnotics is also constrained by their potential for abuse and dependence. The VA/DoD Clinical Practice Guideline discouraged the use of benzodiazepines (BZD) for the treatment of both acute stress disorder and PTSD [64]. Further, starting BZDs prior to CBT for insomnia could blunt the success of behavioral therapy [65]. In contrast, the non-benzodiazepine benzodiazepine-receptor agonists, zolpidem (10 and 20 mg) and eszopiclone (3 mg) were effective in abating symptoms of insomnia in PTSD in small clinical trials [66,67] without the deleterious effect on fear extinction. However, nocturnal complex behaviors, although rare in occurrence, are well-described consequences of these agents and can result in serious injuries [46]. The recently approved orexin receptor antagonists may have a salutatory impact on fear conditioning responses such as reexperiencing symptoms and hyperarousal [47,68], but the efficacy of these agents in this population await the results of ongoing trial (NCT02704754).

3.3. Insomnia in elderly patients with or without dementia

Because of the normal, age-related changes in the diurnal rhythm of several hormones that can affect sleep patterns in the elderly age group, total sleep time and sleep efficiency are decreased with a prominent tendency for early morning awakenings and increased napping

during the day [69]. The multitude of medical conditions most notably chronic obstructive lung disease, congestive heart failure, neurologic conditions, and/or advanced arthritis exacerbates sleep disruption further worsening the severity of insomnia. Instituting pharmacotherapy in this population should rely on comprehensive risk-benefit analysis including assessment of age-related changes of pharmacokinetics and pharmacodynamics. Judicious use of hypnotics can ameliorate the quality of sleep in this age group but the adverse effects can be life threatening due to increased risk of falls, fractures, and worsening delirium [70]. The use of anticholinergics, antipsychotics, doxepin (>6 mg), and benzodiazepines are not recommended in this patient population [71]. However, low-dose doxepin appears to be a good alternative for elderly insomniacs with sleep-maintenance problem [39]. Eszopiclone at a low dose (1 mg) may assist in alleviating sleep onset and sleep-maintenance insomnia up to 12-weeks of use [72]. Alternatively, low-dose suvorexant (10 mg) may be considered. Trazodone produces transient improvement in sleep quality and sleep continuity in older patients with insomnia, but carries significant risks such as orthostatic hypotension and priapism [73,74]. For sleep-onset problem, melatonin, and synthetic melatonin agonists are the preferred therapeutic agents in older adults with insomnia [75,76]. Evidence suggests that prolonged release melatonin may result in significant improvements in sleep quality, sleep-onset latency, and quality of life for patients aged 55 years and older [38,77]. However, these agents should be used with caution in geriatric patients with dementia who exhibit irregular sleep-wake rhythm disorder due to detrimental effects on daytime mood functioning [78].

3.4. Special considerations

Insomnia is a commonly reported sleep disturbance during pregnancy with a prevalence rate ranging from 44% to 75% [79–81]. The rate of insomnia increases progressively throughout pregnancy with the worse symptoms occurring during the third trimester [79,80]. If left untreated, it can lead to perinatal anxiety [82] and post-partum depression [83]. CBT is considered the preferred treatment but pharmacotherapy may be entertained as long as the benefit-risk ratio for maternal and fetal outcomes have been explored with the patient. Diphenhydramine and hydroxyzine are considered the drug of choice during pregnancy; however, it should be acknowledged that there are few studies in humans to confirm their safety profiles. Based on published studies, no adverse perinatal outcomes have been confirmed [84,85]. There are limited data on the use of exogenous melatonin in pregnancy with conflicting results in mouse models [86,87]. Although exogenous melatonin supplementation could impact the density of fetal melatonin receptors, it can exert also neuroprotection in the setting of toxin exposure [86]. Benzodiazepines are occasionally used for anxiety and insomnia in pregnant women. Despite an earlier report of increased incidence of cleft lip with benzodiazepines usage during pregnancy, recent meta-analysis has not confirmed this association [88]. Currently, benzodiazepines are vastly replaced by the Z class drugs (HBRA) [89]. Based on the available research, it would seem that zopiclone and zolpidem can be used as an alternative to antihistamines with both being labeled as pregnancy drug risk category C in the United States [90]. There currently is a paucity of published data from studies that have investigated the effects of antidepressants on pregnancy outcomes. The use of these agents should be made under the supervision of health-care practitioners given the associated risk of low birthweight and preterm birth [91].

Sleep disorders are often inadequately addressed in patients with advanced liver and renal disease. Prescription of hypnotics in these patients should take into account the impairment in clearance and metabolism. In patients with cirrhosis, the selection of a sleeping agent should be chosen among those with negligible hepatic metabolism, short half-life, and limited lipohilia. In renal failure, cutting the dose in half has been advocated for most hypnotics except for ramelteon where no dose adjustment is indicated [92]

4. Conclusions

CBT is considered to be the gold standard in treating insomnia, with similar or greater efficacy than those seen with hypnotic drugs and, unlike with hypnotics, maintenance of effect after cessation of therapy. Pharmacotherapy is considered an alternative approach and selection of appropriate hypnotics should be tailored to the temporal phenotype of insomnia, underlying comorbidities and long-term risk assessment. In primary insomnia, pairing short-term use of pharmacotherapy with some form of CBT can be effective, especially in patients with a low-likelihood of CBT-response. Initiation of hypnotic therapy prior to CBT is not recommended. Long-term use of medications for chronic insomnia should be as an intermittent dosing ‘as needed’ in the setting of maintenance CBT, when possible. Comorbid insomnia should be treated with pharmacotherapy providing dual benefit. More research is needed on the sleep aids that are commercially available and being used regularly without prescriptions.

5. Expert opinion

Both pharmacologic and non-pharmacologic treatment modalities have advantages and shortcomings, and neither approach is effective for all types of insomnia patients. It is difficult to predict a priori the response rate of patients once hypnotics are initiated but residual or recurrent insomnia once these agents are tapered or withdrawn appears to be a common denominator among patients with chronic insomnia. Research to evaluate more efficient models integrating behavioral approaches using multifaceted, sequential therapies [93] has not so far shown superior success over the traditional approach in randomized trials.

Competing arguments on whether fixed versus intermittent dosing strategies for the treatment of chronic insomnia continues to dominate the sleep literature and there is no sign, short of a randomized controlled trial, that the matter will be settled soon. On one hand, it has been posited that it may be more prudent to administer hypnotics on an as needed basis rather than on a fixed nightly schedule because insomnia frequently is not a nightly phenomenon. This would limit total medication exposure and minimize tolerance, dependence, and costs. On the other hand, there are those who speculate, based on conditioning theory, that intermittent use should be avoided and hypnotics should be prescribed as every other night or every third night to reduce the psychological factors that can maintain a focus on pill-taking [94]. Interestingly, no matter whether medications were taken intermittently or nightly, no difference was observed in efficacy, tolerance, or abuse [43].

While benzodiazepines have been the backbone of treatment modalities for insomnia over the last 50 years, the use of these agents should be considered only in specific circumstances such as insomnia complicating REM behavioral disorder or treatment-resistance cases of generalized anxiety disorders and panic disorders. The risk/benefit of these drugs has been tilting toward harm as the list of adverse events continues to grow with the longer use of these medications. Risks include dependence, tolerance, cognitive dysfunction, withdrawal, and suicidal ideations [95]. Over the past decade, reports of an association between prior benzodiazepine-agonist agents intake with cancer incidence had raised concerns about their prolonged use [96,97]. Cumulative data from FDA-approved clinical trials have suggested increased incidence of breast cancer, ovarian cancer, and skin cancers (non-melanoma) among patients receiving benzodiazepines while a small case-control study has linked benzodiazepine to acute myeloid leukemia [98,99]. Further, epidemiological studies have alluded to the fact that the use of benzodiazepine medications were associated with increased mortality [96,100]. Although some of these associations have been disputed because of study design limitations and lack of precise estimates [101], it is important that providers always discuss these concerns with the patient and document their reasoning for the choice of hypnotic(s) prescribed. It should be noted also that Z-drugs have been linked to dementia, delirium, and an increase in motor vehicle accidents [102,103]. However, these associations were based on small effect sizes and studies that displayed a broad range of methodologies and a wide array of subjective outcomes.

With limited access to sleep medicine experts and pervasive consumer advertisements, patients with chronic insomnia often use over-the-counter sleep aids that are readily available without a prescription. Despite the availability of FDA-approved hypnotics and their proven efficacy, approximately half of all physicians are still prescribing off-label antidepressants for insomnia. Anti-histamines like diphenhydramine and doxylamine have predictable sleep promotion but are linked to many side effects (confusion, dry mouth, delirium, constipation, urinary retention). These drugs have long elimination half-lives and often cause next-morning drowsiness [104]. Elderly people are the most vulnerable to these side effects and while there is no systematic evidence for their efficacy, there are significant concerns about their safety [13]. As recommended by the American Academy of Sleep Medicine (AASM) [105], off-label hypnotics may be considered in at least two situations: When FDA-approved drugs are not efficacious for a particular patient and when insomnia coexists with a comorbid condition that may actually benefit from this off-label drug which is FDA approved for the co-morbid condition.

At present, there is inadequate evidence to support the use of melatonin supplement in primary insomnia [106]. Available studies have been inconsistent in design and methodology. For instance, the prescribed dosage ranged from 0.1 to 75 mg and the timing of administration varied from 30 min to 3 h before bedtime [107,108]. Conversely, melatonin may have a substantive therapeutic effect in comorbid insomnia including children with neurodevelopmental disorders [109,110]; however, these benefits are documented in limited number of observations and further investigations may be required before the role of melatonin in comorbid insomnia is established. Melatonin is considered a safe drug and its side effect are not different from placebo [105] although It has been reported that melatonin may temporarily affect fertility in both men and women [111].

Whether a combination of melatonin with other hypnotic agents can assist in alleviating insomnia while reducing side effects remains to be seen.

Last but not least, herbal preparations (e.g., valerian root) are often purchased for the treatment of insomnia. These preparations are not regulated by the FDA and there is not enough evidence to delineate the optimal amount that entails therapeutic benefit. Because of the significant limitations of available studies, we advocate for larger randomized, controlled trails that adhere to established quality guidelines and have adequate power to assess changes in standard, subjective measures of sleep quality and overall quality of life [112].

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Article Highlights

- Insomnia is the most prevalent sleep disorder that can present independently (primary insomnia) or associated with another medical or psychiatric disorders (comorbid insomnia).
- CBT is the recommended first line of therapy for insomnia but barriers to implementation include the scarce availability of qualified providers and perceived stigma by those seeking treatment.
- The choice of drug for insomnia treatment should be based on the pharmacological properties of the agent and the clinical attributes of the patient.
- Use of antidepressants, antipsychotics, and over the counter sedating agents for the treatment of chronic insomnia is not supported by empirical evidence.
- Future research should evaluate targeted therapy based on specific phenotypes using CBT as an augmentation therapy.

Table 1.

Drugs used for the treatment of chronic insomnia[a].

Drug name	SOI	SMI	Dosage (mg)	Adverse events
Z-drugs				
Eszopiclone[b]	•	•	1–3	Metallic taste, dry mouth, nocturnal complex behaviors
Zaleplon[b]	•		5 to 10	Headache, fatigue, somnolence, asthenia
Zolpidem[b]	•		5 to 10	Drowsiness, excessive sleepiness, hallucinations, depression, nocturnal complex behaviors
Zolpidem, CR[b]	•	•	6.25 to 12.5	Drowsiness, headache, next-day somnolence, dizziness
Zolpidem, SL[b]		•[c]	1.75 or 3.5	Drowsiness, excessive sleepiness, hallucinations, depression, nocturnal complex behaviors
Zolpidem, oral spray[b]	•		5–10	Drowsiness, dizziness, diarrhea, drugged feeling
Melatonin agonists				
Melatonin			1	Headache, somnolence
Ramelteon[b]	•		8	paradoxical worsening of insomnia; avoid combination with cytochrome inhibitors especially fluvoxamine; contraindicated in those with severe hepatic impairment
Antidepressants				
Amitriptyline			25 to 150	Orthostatic hypotension, cardiac arrhythmias,
Doxepin[b]			3 to 6	dizziness, dry mouth, blurred vision, constipation, and urinary retention. It should not be co-administered with MAOI and Tolazamide.
Mirtazapine			7.5 to 15	Dry mouth, drowsiness, sedation, weight gain
Nortriptyline			25 to 150	Fatigue, lethargy, constipation, orthostatic hypotension, suicidal ideations
Trazodone			50 to 100	Residual daytime sedation, orthostatic hypotension, headache, nausea, vomiting, xerostomia, priapism
Orexin receptor antagonist				
Suvorexant[b]	•	•	5–20	Somnolence, narcolepsy, headache, dry mouth
Antihistamines				
Diphenhydramine			25 to 50	Somnolence, dry mouth, dizziness, dyskinesia
Doxylamine			25 to 50	Blurred vision, constipation, dizziness, paresthesia, nightmares
Hydroxyzine			50–100	Drowsiness, dry mouth, hallucination
Antipsychotics				
Olanzapine			2.5 to 20	Orthostatic hypotension, dyslipidemia, Type 2 diabetes, weight gain, extrapyramidal symptoms. Gynecomastia, neuroleptic malignant syndrome

Drug name	SOI	SMI	Dosage (mg)	Adverse events
Quetiapine			50 to 400	Orthostatic hypotension, dyslipidemia, weight gain, neuroleptic malignant syndrome, tardive dyskinesia
Risperidone			0.25 to 6	Orthostatic hypotension, ketoacidosis, hyperglycemia, tardive dyskinesia, hyperprolactinemia
Anticonvulsants				
Gabapentin			300 to 600	Drowsiness, somnolence, beneficial inpatients with restless leg syndrome
Pregabalin			50 to 300	Peripheral edema, dizziness, weight gain, blurred vision, seizures, suicidal ideations,

SOI = Sleep-onset insomnia; SMI-Sleep maintenance insomnia; CR = continuous release; SL = sublingual

*[a]The list excludes benzodiazepines

[b]FDA approved drugs

[c]provided four additional hours of sleep/time in bed before planned awakening.