

Sleep Maintenance Insomnia: Strengths and Weaknesses of Current Pharmacologic Therapies

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Background. Although insomnia is highly prevalent, sleep disturbances often go unrecognized and untreated. When insomnia is recognized, considerable emphasis has been placed on improving sleep onset; however, there is growing evidence that improving sleep maintenance is an equally important treatment goal.

Methods. A MEDLINE literature search was performed using the search parameters “insomnia,” “zolpidem,” “zaleplon,” “flurazepam,” “estazolam,” “quazepam,” “triazolam,” and “temazepam,” as these agents are FDA-approved for the treatment of insomnia. Per reviewer comments, the search criteria was later expanded to include lorazepam. A literature search using the terms “trazodone” and “insomnia” was also performed, as this is the second-most commonly prescribed agent for treating insomnia. Sleep efficacy endpoints from randomized, placebo-controlled clinical trials in adult populations and key review articles published between 1975 and 2004 were included in this review. As only one randomized placebo-controlled trial evaluated trazodone use in primary insomnia, the trazodone search was expanded to include all clinical trials that evaluated trazodone use in insomnia. Relevant texts and other articles that evaluated side effect profiles of these agents were also included, one of which was published in January of 2005. In all publications, impact of treatment on sleep maintenance parameters (wake time after sleep onset, number of awakenings) and measures of next-day functioning were evaluated, in addition to sleep onset parameters (sleep latency, time to sleep onset/induction) and sleep duration data (total sleep time).

Results. Many of the currently available agents used to treat insomnia, including the antidepressant trazodone, the non-benzodiazepine hypnotics zolpidem and zaleplon, and some of the benzodiazepines, have not consistently demonstrated effectiveness in promoting sleep maintenance. Furthermore, the benzodiazepines with established sleep maintenance efficacy are associated with next-day sedation, the risk of tolerance and dependence, or both.

Conclusions. New agents that offer relief of sleep maintenance insomnia without residual next day impairment while improving next day function are needed. Several compounds currently under development may offer clinicians a more effective and safer treatment for this common disorder.

Keywords Insomnia, Sleep maintenance, Benzodiazepines, Non-benzodiazepines, Trazodone, Eszopiclone

INTRODUCTION

Approximately 10% to 15% of adults suffer from chronic insomnia, and an additional 25% to 35% have transient or occasional insomnia (1). Some data suggest that while the prevalence of insomnia has increased in recent years, insomnia nevertheless remains underrecognized, underdiagnosed, and undertreated (2–4), quite possibly because providing effective treatment is a continuing challenge for healthcare providers.

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The current armamentarium does not offer an optimal balance between the tolerability profile (including next-day residual effects) and the efficacy profile, particularly in the area of sleep maintenance and long-term use. Furthermore, although current non-benzodiazepine medications for insomnia are often useful in alleviating sleep onset difficulties, they are less useful in treating sleep maintenance problems. This weakness in insomnia treatment options is problematic in light of the emerging consensus among sleep specialists that improving sleep maintenance (the ability to sleep without persistent interruptions or extended periods of wakefulness) should be a target for treatment (5,6). A number of studies have shown that many patients with transient and chronic

insomnia have sleep maintenance difficulties, especially in certain population groups, such as the elderly, and those with physical illnesses (5–8).

A medication that reduces time to sleep onset, improves sleep maintenance, and avoids next-day residual effects, as well as, ideally, enhancing daytime functioning, represents an optimal approach to treating insomnia (9–11). This review offers a brief discussion of the definition of insomnia and the associated difficulties, and emphasizes the importance of attention to sleep maintenance problems. In addition, the efficacy of current FDA-approved pharmacologic therapies and commonly used non-approved medications in maintaining sleep, and resultant next-day functioning are reviewed.

DEFINING AND DIAGNOSING INSOMNIA

According to the American Psychiatric Association (APA) a diagnosis of primary insomnia must meet the criteria outlined in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* [DSM-IV] (12): (A) predominant complaint is difficulty initiating or maintaining sleep or nonrestorative sleep for at least 1 month; (B) the sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning; (C) the sleep disturbance does not occur exclusively during the course of narcolepsy, circadian rhythm disorder, or a parasomnia; (D) the disturbance does not occur exclusively during the course of another mental disorder (e.g., major depressive disorder, generalized anxiety disorder, or delirium); (E) the disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse or a medication) or a general medical condition. The APA defines secondary insomnia as insomnia related to another mental disorder; a sleep disorder due to a general medical condition, insomnia type; or a substance-induced sleep disorder, insomnia type. Insomnia can also occur comorbid to another disorder.

Generally, patients with insomnia, whether primary or comorbid, are further divided into groups based on when their sleep difficulty most often occurs. The three categories are (1) sleep onset insomnia (difficulty in falling asleep); (2) sleep maintenance insomnia (difficulty staying asleep); and (3) terminal insomnia (early-morning awakenings coupled with an inability to return to sleep). These symptoms may occur singly or in combination, as is the case in many patients with chronic insomnia, which may result from several different etiologies (13). These patients often have several sleep complaints simultaneously and experience a gamut of sleep disturbances, including prolonged latency to sleep onset, increased time awake during the sleep period, and reduced total sleep time (14). Patients may not always volunteer such information without prompting, however, especially in the context of a severe condition, such as depression or anxiety.

Insomnia symptoms also tend to vary over time (15). A study by Hohagen and colleagues in 328 adults who experienced

disturbed sleep at least 3 times a week for 4 weeks or longer found that insomnia symptoms did not remain stable over a period of 4 months. At an initial inquiry, and again 4 months later, patients completed a questionnaire that described their sleep problems as characterized by one or more of the following: difficulty falling asleep, waking during the night and having trouble returning to sleep, or waking earlier than desired. The majority of patients were found to have fluctuations in their insomnia symptoms after 4 months, with only 35% of patients reporting the same sleep complaint at follow-up and only 13% of patients overall experiencing a remission of symptoms (15).

An initial diagnosis can usually be made by obtaining a sleep history, which provides the clinician with information pertinent to the nature, severity, and duration of the patient's sleep problem. This can be done with or without the aid of standardized sleep questionnaires, such as the Pittsburgh Sleep Quality Index. Polysomnography (PSG) can also be used to obtain a more quantitative measure of the problem. However, according to the American Academy of Sleep Medicine, PSG is not recommended for routine evaluation of insomnia (16).

When quantifying sleep maintenance difficulties via PSG, wake time after sleep onset (WASO) and number of awakenings (NAW) are the most commonly utilized parameters. WASO is a robust measure of sleep maintenance, as it represents the total amount of time spent awake after the person has fallen asleep, while NAW represents only the number of awakenings the person has experienced. Therefore, a person may wake only once during the night (NAW), but may spend 3 hours awake (WASO), so the latter measure more closely reflects the level of disturbance.

Prevalence of Sleep Maintenance Problems

According to a survey conducted by the National Sleep Foundation, which assessed the occurrence of 4 symptoms of insomnia in adults in the United States (difficulty falling asleep; waking often during the night; waking up too early and not being able to get back to sleep; and waking up feeling unrefreshed), sleep maintenance issues were reported more often than sleep onset issues (8). Specifically, of those reporting insomnia symptoms at least a few nights a week within the past year; 25% reported difficulty falling asleep, and 60% reported being awake often during the night or waking up too early and being unable to fall back asleep.

As mentioned previously, sleep maintenance problems are more prominent in certain population groups (5,6). In the elderly, poor sleep maintenance is the most common complaint (17–20). Problems with sleep maintenance are also the primary insomnia symptoms in depressed (19–22) and medically ill populations (23), especially those with pain syndromes (24–26). Insomnia (27,28) and, indeed, sleep maintenance problems (or sleep fragmentation) (29) are also commonly seen in perimenopausal women.

Treating Insomnia

Characteristics of an effective hypnotic would include the ability to reduce sleep latency, increase total sleep time, increase sleep maintenance without next-day residual effects, and enhance daytime functioning (Table 1) (3,11,30). Currently available hypnotic agents do not adequately fulfill these needs in the absence of side effects, drug-drug interactions, or development of tolerance (31,32).

Early hypnotics (namely, benzodiazepines) were effective, but they were associated with residual effects and the risk of abuse and dependence (14). More recently, there has been a drive to reduce next-day residual effects by using agents with shorter half-lives (30,33,34). Newer hypnotics are generally effective in reducing time to sleep onset (i.e., decreasing sleep latency), but they have been found to be less effective at improving sleep maintenance (35–38), leaving clinicians uncertain about how to provide appropriate care for patients with sleep maintenance problems.

Both the dose and the half-life are important determinants of a hypnotic agent's tendency to cause next-day residual effects. Thus, the trend in the development of sleep aids, beginning with the initial introduction of the benzodiazepines as hypnotics in 1970, has been toward compounds with shorter and shorter half-lives (30,39) (see Table 2). In a study of benzodiazepine and non-benzodiazepine hypnotics, Wheatley found a good correlation between half-life and improvements

on PSG sleep parameters, such as time asleep and number of awakenings (40). Reducing the half-life will reduce the time that the patient is sedated, thereby reducing the risk of next-day sedation-related impairment (41). A drug's therapeutic dose is another correlate of next-day impairment, with higher doses corresponding to a greater level of residual sedation, and therefore agents with the lowest possible effective doses are desirable (39,41).

Zolpidem

Zolpidem is currently the most commonly prescribed hypnotic (42). Zolpidem's short half-life (1.5 to 2.4 hours) (43) likely contributes to its relatively low incidence of residual effects as compared with benzodiazepines (44), and may also limit its ability to maintain sleep (45). In general, randomized, controlled clinical trials have shown that zolpidem improves sleep latency and sleep duration (35,37,38,46–49). However, in the 10 of the 10 studies found, WASO and/or NAW were either not assessed or not improved/sustained compared with placebo (35,38,46–48,50,51). In a 2-week study there were statistically significant improvements compared with placebo in NAW and WASO during week 1 that were not sustained in week 2 (36). Similarly, in a 4-week study, improvements in NAW week 1 and 2 were not sustained during weeks 3 and 4; WASO was not reported (38). Randomized, controlled, nightly dosing trials have not exceeded 5 weeks; however one

Table 1 Treatment Profiles of Currently Available Agents

	Sleep onset	Sleep maintenance	Next-day residual effects	Rebound, tolerance, dependence	Improved next-day function
Ideal agent (52)	Yes	Yes	No	No	Yes
BZDs (128)	Yes	Yes	Yes	Yes	No
Trazodone (64-66)	?	?	Yes	Yes/?	No
Zolpidem (58,130)	Yes	?	?	No/?	?
Zaleplon (128)	Yes	No	No	No	?

Table 2 Pharmacokinetic Variables of Hypnotic Agents

Agent	Elimination Half-life (hrs)	Clinical Implications
Benzodiazepine hypnotics:		
Temazepam	10-40	After repeated dosing, agents with long $t_{1/2}$ (>8 hrs) more likely to produce daytime cognitive or psychomotor side effects; agents with very short $t_{1/2}$ (<4 hrs) more likely to produce breakthrough or rebound insomnia or anxiety.
Triazolam	2-3	
Estazolam	10-24	
Flurazepam	40-100	
Quazepam	30-100	
Zolpidem	1.5-3.5	Short $t_{1/2}$ may reduce next-day side effects, but limit effect on sleep maintenance; may not reduce WASO.
Zaleplon	1	Short $t_{1/2}$ may reduce next-day side effects, but limit effect on sleep maintenance; may not reduce WASO.
Trazodone	3-9	In theory, mean $t_{1/2}$ is optimal for sleep maintenance without daytime residual effects; however, mCPP metabolite may cause anxiety/insomnia in some patients.

Abbreviations: $t_{1/2}$ = half-life; WASO = wake time after sleep onset.

intermittent dosing study (49) was of 12 weeks duration. (49). None of these randomized, controlled studies either assessed or reported issues with withdrawal; however, findings concerning tolerance and rebound insomnia were inconsistent (35–38).

Zaleplon

Zaleplon, the other non-benzodiazepine hypnotic currently approved for the treatment of insomnia, has an even shorter half-life than zolpidem (approximately 1 hour) (52). In healthy subjects (53,54) and in patients with insomnia (55), it was not found to cause residual daytime memory impairment. Zaleplon has been shown to improve sleep onset in 3 large randomized, controlled subjective trials in patients with insomnia (37,38,56); however, there was no evidence that zaleplon improves sleep maintenance at the 10 mg dose. A smaller randomized, controlled, double-blind trial used both objective and subjective measures to compare 4 doses of zaleplon (10, 20, 40, and 60 mg) with triazolam and placebo (55). All doses significantly improved sleep latency, but increases in total sleep time were seen only at the highest dose of 60 mg (55). Though randomized, controlled studies with zaleplon do not exceed 4 weeks, there does not appear to be rebound insomnia, withdrawal symptoms, or tolerance with zaleplon use.

Trazodone

The sedating antidepressant trazodone is the second-most frequently prescribed agent for insomnia (42) possibly because, as an unscheduled drug, it has a low potential for abuse (3) and is perceived as safe and effective in the treatment of insomnia. However, since 1980, fewer than 60 subjects treated with trazodone have been assessed with PSG for evidence of improved sleep onset and/or maintenance (57–62). Two of the studies were ≤ 1 week in duration (57,62); the remaining five ran 3–8 weeks (58–60,61,63). Patient populations consisted of 6 to 11 patients (57–62), none of whom had been diagnosed with primary insomnia; all but 9 (58) of whom had sleep disturbances secondary to depression. For doses ranging from 200 to 600 mg, sleep latency was significantly improved (61,63). Significant reductions in NAW were seen at doses of 50–600 mg (57,58,61–63), while doses of 100–600 mgs demonstrated significant increases in TST (57,61,63). However, study limitations (sample size, range in doses and patient diagnosis) make it difficult to generalize these findings to non-depressed insomniacs. In the only trial assessing trazodone in primary insomnia, patients received 2-weeks of trazodone (50 mg), zolpidem (10 mg), or placebo (64). Significant improvements in self-reported sleep latency and sleep duration were noted with both drugs during Week 1. Trazodone and placebo did not differ during Week 2, but the absence of statistical significance during Week 2 appeared to be due primarily to improvement in the placebo group. Some or all of the following side effects: dizziness, dry mouth, headache, nausea, blurred vision, drowsiness, hypotension, psychomotor impairment, and

rebound insomnia have been associated with trazodone use in healthy patients, depressed patients, and patients with insomnia (64–66). In addition, trazodone's association with potentially fatal QT-prolongation (67) has been further corroborated by an in vitro study, which concluded that trazodone appears to prolong the QT-interval via inhibition of I_{Kr} , which is the most common cause of QT- interval prolongation by non-cardiac drugs (68,69).

Benzodiazepines

Currently approved benzodiazepines for the treatment of insomnia are flurazepam, triazolam, quazepam, estazolam, and temazepam. These agents have generally been found to be effective in improving sleep onset and sleep maintenance (70–90). Lorazepam, commonly used to treat secondary insomnia off-label, has demonstrated some efficacy in sleep maintenance (91), but not sleep onset (91,92). The clinical usefulness of this class of agents, however, is hindered by safety and tolerability concerns such as next-day sedation (93, 94), impaired delayed and immediate recall (95), cognitive impairment (96), and risk for abuse and dependence (44). It is thought that the development of dependence is mediated through a combination of several effects: tolerance, early morning insomnia, daytime anxiety, and rebound insomnia and anxiety (44,97). In general, benzodiazepines with shorter half-lives, such as triazolam and temazepam, are considered to be more likely to cause rebound insomnia and withdrawal symptoms, while those with longer half-lives, such as flurazepam, temazepam, and quazepam, are viewed as more likely to cause next-day "hangover" effects, daytime somnolence and/or decreased performance on psychomotor tests (68–70,75,77,86–88,98–104).

Temazepam is the most commonly used benzodiazepine hypnotic (42) and the third-most commonly prescribed agent for insomnia. In 5 of 9 studies of temazepam where sleep onset, sleep maintenance and total sleep time parameters were assessed, patients demonstrated significant improvement in all three domains (32,105–108); however in two studies, temazepam demonstrated no significant difference in any of those domains (109,110). In studies where results were mixed, three studies demonstrated improvements in onset and TST but not maintenance as defined by number of awakenings (111,112). The tenth study, which only assessed TST, temazepam demonstrated significant improvements versus baseline (113).

Opportunities for Improving Sleep Maintenance

Newer agents for the management of insomnia deserve mention. These include the new modified-release formulation of zolpidem (114), melatonin agonists, such as TAK-375 (115,116), other non-benzodiazepines such as indiplon (117–119), and eszopiclone (120–123), a pyrrolopyrzzine derivative of the cyclopyrrolone class, and the only non-benzodiazepine indicated for both sleep onset and sleep maintenance insomnia.

CONCLUSIONS

Adequate recognition of sleep difficulties is an important unmet medical need. Difficulty with maintaining sleep is common in patients with medical and psychiatric disorders, as well as in patients with primary insomnia, and it occurs with more frequency than sleep onset problems in certain population groups. Given the high prevalence rates of insomnia in the elderly (17,124) and the continued growth of the elderly population in the United States (125), sleep maintenance difficulties in this population segment represent an increasingly serious healthcare concern. However, currently used medications fall short when it comes to safely and effectively addressing sleep maintenance problems.

Interestingly, there is currently no consensus among sleep specialists and other experts regarding treatment of chronic insomnia and long term use of hypnotics. A rational pharmacological approach to treating chronic insomnia is to prescribe nightly or near nightly use of a non-benzodiazepine hypnotic for a period of one to two months and then reassess. Beyond this initial period of consistent hypnotic use, patients should be encouraged to maintain behavioral changes and to use hypnotics on a more targeted or intermittent basis (e.g., 4–5 nights per week) if possible. Provided patients adhere to prescription directives, ongoing, indefinite use is reasonable.

Eszopiclone is the only hypnotic approved for long-term use. In a 6-month double blind study with a 6-month open label extension, eszopiclone was shown to be safe and effective, as demonstrated by significant improvements in sleep onset, sleep maintenance and sleep duration, without tolerance or significant rebound (121). Other currently available non-benzodiazepine hypnotics zolpidem (35,36,46,) and zaleplon (37,38,56) have shown positive effects on sleep latency, but have been inconsistent in demonstrating improved sleep maintenance at recommended doses by subjective measures; and improvement in sleep maintenance has not been demonstrated via PSG in randomized, controlled trials. The efficacy of trazodone for insomnia has yet to be established in randomized, controlled trials; and it is associated with numerous side effects (126). The benzodiazepine class of agents, though effective in improving sleep (91,127), displays a variety of unwanted residual or side effects (rebound, tolerance, or dependence) (44,91,93,94,128). Given this lack of consistent evidence of efficacy and tolerability, and the fact that temazepam, trazodone, and zolpidem together account for 96% of prescriptions for insomnia medication (42), additional pharmacological options offering a more optimal profile would be well received. Development of an optimal pharmacologic treatment will require agents that improve sleep maintenance, sleep onset, and sleep quality while also improving daytime functioning. Furthermore, because some patients with chronic insomnia may require long-term treatment with hypnotic agents, it is important that agents used in treating insomnia are shown to be effective and safe in the long term and are demonstrated not to be associated with symptoms of tolerance or

dependence. Newer agents show some promise in addressing these treatment challenges. It is also important to mention that while the focus of this paper has been on pharmacologic interventions and, therefore, non-pharmacologic interventions have not been discussed, these should be considered in the management of all patients, as they can be very effective (129,130).

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