Current Patterns and Future Directions in the Treatment of Insomnia

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Background. Despite the high prevalence and the high burden associated with chronic insomnia, it remains largely unrecognized and often inadequately treated by physicians.

Methods: A review was undertaken of the literature on barriers to both acute and chronic treatment of insomnia, as well as recent trials of pharmacologic and nonpharmacologic agents for insomnia.

Results. Obstacles to appropriate treatment of the condition include outdated insomnia management guidelines, which have contributed to US Food and Drug Administration restrictions on longer-term prescription of hypnotic agents; lack of research demonstrating the benefit of treating insomnia; and fears of tolerance and withdrawal effects of long-term use of hypnotic agents, as well as an absence of longer-term, randomized, controlled, double-blind trials of existing agents used to treat insomnia.

Conclusions. There is evidence that improved sleep may improve outcome in some medical and psychiatric illnesses. Both behavioral and pharmacologic therapies have shown efficacy in chronic insomnia. In addition, a recent 6-month, randomized, controlled study has demonstrated that at least one agent may be safe and effective in longer-term use.

Keywords Chronic insomnia, Sleep maintenance, Trazodone, Benzodiazepines, Non-benzodiazepines

INTRODUCTION

Prevalence rates for insomnia in general community surveys range from 9% to 36% (1–4). As insomnia is a symptom of numerous medical and psychiatric illnesses (5,6), prevalence rates reported in clinical settings are understandably higher, ranging from 10% to 50% (6–10). In addition, population surveys indicate that of the approximately 50% of the general population who report sleep difficulties, 20% to 36% report a duration of such difficulties of more than 1 year (11–14). Since many psychiatric patients have insomnia, and psychiatrists are frequently consulted regarding individuals with chronic insomnia, it is particularly important that psychiatrists understand and treat insomnia effectively.

While there are many ways of classifying insomnia, the first step in a psychiatrist’s algorithm is the duration of the insomnia complaint (15). Unfortunately, commonly used classification systems for insomnia do not aid with determination and definition of chronicity. The International Classification of Sleep Disorders (ICSD) (16) distinguishes duration of insomnia by a number of different subtypes, making its use very cumbersome in the clinical setting. The Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) (17) does not use duration as a determining criterion for its classification scheme; rather, it divides sleep disorders into “Primary Sleep Disorders,” “Sleep Disorders Related to Another Mental Disorder,” and “Other Sleep Disorders,” including those caused by general medical conditions. However, DSM-IV-TR’s criterion A for primary insomnia requires “…a complaint of difficulty initiating or maintaining sleep or of nonrestorative sleep that lasts for at least 1 month” (17) (see Table 1). Various definitions of acute and chronic insomnia have been put forward, with acute insomnia generally lasting no more than 2 weeks,
Table 1  Diagnostic Criteria for Primary Insomnia from the DSM-IV-TR

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<td>A.</td>
<td>The predominant complaint is difficulty initiating or maintaining sleep, or nonrestorative sleep, for at least 1 month.</td>
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<td>B.</td>
<td>The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.</td>
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<tr>
<td>C.</td>
<td>The sleep disturbance does not occur exclusively during the course of Narcolepsy, Breathing-Related Sleep Disorder, Circadian Rhythm Sleep Disorder, or a Parasomnia.</td>
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<td>D.</td>
<td>The disturbance does not occur exclusively during the course of another mental disorder (e.g., Major Depressive Disorder, Generalized Anxiety Disorder, a delirium).</td>
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<tr>
<td>E.</td>
<td>The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.</td>
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and chronic insomnia lasting 3 to 4 weeks or longer (18, 19). The DSM-IV-TR construct of primary insomnia, therefore, appears to subsume most definitions of chronic insomnia.

Insomnia, by DSM-IV-TR criteria, involves difficulty initiating sleep (sleep onset problem); maintaining sleep; or obtaining restorative sleep. Sleep maintenance problems may take several forms—for example, prolonged wakefulness, frequent awakenings, and/or nonrestorative sleep. In addition, for a DSM-IV-TR diagnosis of insomnia, daytime dysfunction or distress is required, which usually takes the form of dysphoria, hyperarousal, or diminished function while awake (20). Of note, self-reports of patients’ sleep may be inconsistent with polysomnographic recordings generated on the same night (21), demonstrating that sleep has both an objective and a subjective basis.

Insomnia symptoms often change over time in those with chronic insomnia (14). The presence of symptom variability in individual patients over time (i.e., changes from sleep onset to sleep maintenance insomnia, to insomnia with early morning awakening, or vice-versa) may have important implications for treatment of chronic insomnia. Although many physicians focus on treatments that address sleep onset difficulties, both psychiatrically and medically ill patients with chronic insomnia frequently experience sleep maintenance problems (8, 22–28). Treatments that have demonstrated the ability to improve both sleep onset and sleep maintenance problems and improve next-day symptoms over the long term, without causing adverse next-day effects, remain an unmet need (29).

**Burden of Chronic Insomnia**

It is crucial that insomnia be viewed not only as a complaint of sleep disturbance or a measurable sleep impairment (in a laboratory setting), but also as an impaired capacity to function normally as a result of sleep difficulties. Studies have demonstrated that the life burden related to insomnia is substantial and that chronic insomnia reduces the ability to cope, accomplish tasks, and deal with personal relationships and family and social life (30). Insomnia sufferers report becoming more readily annoyed, upset, or irritated, feeling tired, and having difficulty remembering (31). They also subjectively report difficulties with psychomotor functioning, including impaired memory, concentration, attention, reasoning, problem solving, and reaction time (32). Impairments in cognitive function (33, 34), such as impairments in short-term and semantic memory, as well as confusion, have been objectively documented in association with sleep deficits. This impaired functioning has substantial implications. Individuals with insomnia use healthcare services more frequently (7, 35), have more days with limited activity, and spend more days in bed due to illness than those without insomnia (7). Studies have also shown reduced productivity (36), higher rates of absenteeism (37), increased accident risk (31, 38), and lower quality of life measures among chronic insomnia sufferers (39, 40).

Aside from the direct consequences of insomnia, there is also evidence that individuals with insomnia are at higher risk for development of depression (35, 41, 42) and depressive relapse (43). Ford and Kamerow (35) found that the odds of developing depression were 20 times higher if insomnia was experienced during the preceding year than if insomnia was absent. Breslau et al. found that sleeping difficulty predicted depression, even in the absence of other depressive symptoms (odds ratio [OR], 2.1) (42). Insomnia associated with depression increases the risk of adverse events, such as suicide (44–46) and resistance to cognitive behavioral therapy (45), as well as relapse (43, 47). Emerging evidence suggests that insomnia worsens outcome in medical illnesses; for example, one recent report demonstrated that chronic sleep difficulties predicted mortality related to coronary artery disease in males (48).

**Insomnia Is Underrecognized and Undertreated**

Insomnia is underdiagnosed. The World Health Organization’s international collaborative study on healthcare attendees in 15 primary care sites found that physicians detected insomnia in less than 50% of patients with insomnia symptoms (49). It appears that both patients and physicians may not recognize the need to discuss sleep disturbances during office visits. Shochat and colleagues (8) found that only 30% of patients with sleep difficulties seen in primary care clinics had ever spoken with their physician about a sleep problem and reported that they were the first to raise the issue. Ford and Kamerow (35) found that of those among their subjects who reported “difficulty sleeping,” only 9% had mentioned the problem to a physician. An Australian study (50) determined that, among hospitalized patients, reference to sleep was recorded in only 9% of patients’ notes. There is also evidence that insomnia is undertreated. The 2002 Sleep in America Poll conducted by the National Sleep Foundation (51) demonstrated that of those who reported experiencing insomnia, only 15% reported using any medication to help them sleep (both physician-prescribed...
Conference established guidelines for the management of these patients. Treatment may be necessary and/or indicated. On the other hand, there are many obstacles to longer-term treatment of these patients.

The 1983 National Institutes of Health (NIH) Consensus Conference established guidelines for the management of insomnia (54), which have largely been responsible for the establishment of restrictions on longer-term prescription of benzodiazepine and non-benzodiazepine hypnotics by the US Food and Drug Administration (FDA) (55). Current FDA-approved product labeling for hypnotic agents specifies short-term use (i.e., up to 1 month of use for benzodiazepine and non-benzodiazepine hypnotics) (55). Although these guidelines have been declared to be outdated by the NIH (http://consensus.nih.gov/cons/039/039_intro.htm), they have not been updated since 1983. FDA restrictions also have not been updated since NIH guidelines were instituted; are based largely on concerns regarding risks of abuse and dependence associated with benzodiazepines at the time (56); and persist despite developments in the field of insomnia over the last 20 years. More recent evidence suggests that patients with insomnia use hypnotic medications for therapeutic reasons and not due to drug-seeking behavior (57–60).

Lack of recognition of the longer-term consequences of insomnia and, similarly, the paucity of research demonstrating that there is in fact a benefit to treating insomnia, whether primary or secondary (44,61,62), have also contributed to inadequate treatment of this condition.

Reticence among physicians to recommend hypnotic medication for the longer term is also related, until recently, to the lack of randomized, controlled safety and efficacy trials lasting longer than 12 weeks. This also possibly contributes to the preference for use of antidepressants such as trazodone over hypnotics for insomnia management (63). Antidepressants are perceived as safer agents, despite the fact that they have also not been evaluated for longer-term use in insomnia. In addition, existing medications, while effective from a number of perspectives, also have various shortcomings, which may interfere with physicians’ belief in their capacity to treat the patient with insomnia.

Obstacles to Longer-term Treatment of Insomnia

When one considers the duration of insomnia experienced by many insomnia sufferers and the fact that insomnia is associated with a number of individual (31,33,34,36,37,51) and socioeconomic consequences (37,52), as well as the fact that treatment of chronic insomnia may improve daytime functioning (53), it would seem apparent that longer-term treatment may be necessary and/or indicated. On the other hand, there are many obstacles to longer-term treatment of these patients.

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Pros and Cons of Available Treatments for Chronic Insomnia

Behavioral and Cognitive Behavioral Therapies

There is evidence that use of nonpharmacologic therapies improves insomnia in as many as 70% to 80% of cases; however, treatment response is highly variable (64). Therapies currently accepted as efficacious or probably efficacious by the American Psychological Association include stimulus control, progressive muscle relaxation, paradoxical intention, sleep restriction, biofeedback, and multifaceted cognitive-behavior therapy (64). In a recent meta-analysis (65), cognitive-behavioral therapy showed significant benefit for chronic insomnia, including positive effects on number of awakenings and wake time after sleep onset (WASO), although benefits for total sleep time are less robust. There is also evidence that behavioral and pharmacologic therapies and a combination of the two are equally effective over 4 to 8 weeks of treatment (66); however, longer-term studies (6–24 months) show that improvement associated with pharmacologic therapy is limited to its period of administration, whereas behavioral therapies have persistent beneficial effects (64,66). On the other hand, there is evidence that application of such interventions is difficult, especially in the primary care setting (67), though steps are being taken to increase their use in this environment (67).

Pharmacologic Therapies

Hypnotic agents are needed that improve sleep maintenance and quality of sleep, decrease sleep latency, and increase total sleep time (15), while improving next-day functioning. In addition, hypnotic agents that have a low potential for next-day cognitive side effects, tolerance, and abuse, even after long-term use, are needed. Finally, agents are needed that reduce insomnia in special populations, such as those with depression, anxiety disorders, and medical illness, which do not adversely affect next-day function or underlying medical problems, such as reduced respiratory drive. Although some newer non-benzodiazepine agents may fulfill some of these requirements, they are still far from ideal hypnotic agents (see Table 2).

Two studies offer the suggestion that treatment aimed primarily at reducing insomnia (and perhaps also anxiety) may have adjunctive benefits in the treatment of depression. A randomized, placebo-controlled study comparing the effects of fluoxetine plus clonazepam versus fluoxetine plus placebo in the treatment of adult outpatients with symptoms of anxiety, depression, and sleep disturbance was conducted to explore this (86). Cotherapy with clonazepam accelerated improvement of the core symptoms of depression (depressed mood, guilt, suicide, and loss of interest) provided by fluoxetine over 21 days of treatment. Moreover, adding clonazepam decreased anxiety and sleep disturbances. In another study, Levitan et al. (87) added the amino acid and hypnotic agent tryptophan to fluoxetine in the treatment of major depression. During the first week of
### Table 2  Pros and Cons of Currently Available Agents Used for Insomnia (68–85)

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<th>Agent or chemical class</th>
<th>Potential advantages</th>
<th>Potential disadvantages</th>
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<tr>
<td>Trazodone (Refs. 71–74).</td>
<td>May improve TST and sleep latency in depressed patients and those with insomnia. Low risk of abuse.</td>
<td>No robust, controlled, or long-term (&gt;2-week) studies demonstrating efficacy for sleep maintenance, especially in patients with primary insomnia, at doses used for insomnia. Potentially serious side effects (eg., priapism, cardiac arrhythmias) and drug-drug interactions.</td>
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<td>Benzodiazepines (temazepam, flurazepam, quazepam, triazolam, estazolam) (Refs. 68–69).</td>
<td>Efficacy demonstrated for increasing TST. Anxiolytic effect may be useful for patients with comorbid anxiety disorder. Most BZDs are relatively non-toxic, with few severe drug-drug interactions (except with alcohol, CNS suppressants).</td>
<td>Small effect on time to sleep onset. No controlled studies showing BZD hypnotic efficacy &gt;12 weeks. Benzodiazepines may be associated with next-day sedation, impaired memory, risk of falls, respiratory suppression, tolerance, abuse, and dependence. Short-acting agents may be associated with rebound insomnia and withdrawal syndromes. Drug interactions reported with triazolam.</td>
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<tr>
<td>Zolpidem (Refs. 75–78).</td>
<td>Effective for sleep latency. No accumulation of drug, due to short half-life. Fewer daytime residual effects than long half-life benzodiazepines. May result in less rebound insomnia than triazolam.</td>
<td>Data are weak for improving TST. No evidence of benefit for maintaining sleep in randomized, controlled clinical trials. Absence of longer-term (&gt;5-week) studies of continuous use. After drug administration, dose-related effects on performance tasks and memory comparable to benzodiazepines; sensory/perceptual distortions reported. Abuse, dependence, withdrawal effects, rebound insomnia occasionally reported.</td>
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<tr>
<td>Zaleplon (Refs. 79–82).</td>
<td>Reduces sleep onset insomnia and subjective sleep latency. No accumulation of drug, due to short half-life; minimum of next-day side effects or residual sedation. Has relatively low rate of rebound insomnia and withdrawal on discontinuation.</td>
<td>No evidence from randomized, controlled studies that zaleplon reliably improves sleep maintenance or that hypnotic efficacy persists after 28 days. Drug interactions reported leading to increased zaleplon blood levels.</td>
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<td>Over-the-counter antihistamines (diphenhydramine, doxylamine) (Refs. 83–85).</td>
<td>Placebo-controlled studies suggest modest, short-term (&lt;2-week) benefits on sleep latency, number of awakenings, duration of sleep, improvement in depth and quality of sleep.</td>
<td>No recent controlled studies demonstrating long-term (&gt;3-week) efficacy of diphenhydramine for objectively determined measures of sleep maintenance. Evidence of tolerance after only 3 days; cognitive side effects Drug-drug interactions; potential toxicity with overdose with diphenhydramine and doxylamine.</td>
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Hence, the available evidence fails to demonstrate that diphenhydramine and related over-the-counter antihistamines are viable treatments for providing long-term treatment in chronic insomnia. In addition, adverse effects associated with diphenhydramine, especially in the elderly, are significant and include next-day neurocognitive deficits, including impaired mental performance and automobile driving ability (94), risk of toxicity (83,84,95), drug-drug interactions (96), and anticholinergic effects.

For carefully selected insomniac patients, herbal remedies for insomnia (e.g., valerian) may be considered. However, the safety and efficacy of herbal agents remains uncertain (97), and several herbal agents have the potential for serious side effects and drug-drug interactions (98).

**Benzodiazepine Hypnotics**

Currently, FDA-approved benzodiazepine hypnotics include temazepam, triazolam, estazolam, quazepam, and flurazepam. Aside from triazolam, these agents have half-lives ranging from 10 to 100 hours, which likely improves their capacity to maintain sleep throughout the night (99–103). A recent meta-analysis (70) of benzodiazepine trials for insomnia, which included 45 randomized, controlled trials and a total of 2672 subjects, indicated that while benzodiazepines, compared with placebo, increased total sleep time on polysomnographic measures by 61.8 minutes (95% CI, 37.4 to 86.2), they decreased time to sleep onset by only 4.2 minutes on average (95% CI, -0.7 to -9.2). In this meta-analysis, benzodiazepines decreased subjective sleep latency by 11.7 minutes (95% CI, 7.6 to 15.8). Benzodiazepines may also be associated with impaired delayed and immediate recall (104–106), cognitive impairment (107–110), and risk for rebound insomnia and withdrawal symptoms, depending on the half-life of the medication and the duration of use (111). Triazolam’s shorter half-life may also increase the risk of rebound insomnia (112,113). Long-acting, and possibly even shorter-acting, benzodiazepines also appear to be associated with increased risk of falls, particularly in the elderly (114,115).

Despite their frequent use for treating insomnia, no benzodiazepine has been evaluated in randomized, controlled trials exceeding 12 weeks (116); therefore, efficacy and safety in the longer term have not been evaluated.

**Non-benzodiazepine Hypnotics**

The advent of the non-benzodiazepine hypnotics zaleplon (81,82) and zolpidem (71,75) resulted in a reduced risk of next-day residual effects, based on their shorter half-lives (1 hour and 2.5 hours, respectively). Even middle-of-the-night dosing with zaleplon has not been associated with next-day residual effects (117), and it has been approved by the FDA for this indication. However, shorter half-lives have meant reduced efficacy in treating sleep maintenance problems, as measured by number of awakenings and WASO. This has been demonstrated in randomized, controlled, objective and patient-reported trials of zaleplon (81,82) and zolpidem (71,75,77,118). Compared to benzodiazepines, these agents generally have a better safety profile (119,120), though there have been reports of negative, dose-related effects on performance tasks (121). Hallucinatory phenomena and other sensory distortions have also been reported in those awake after medication administration, even with therapeutic doses of zolpidem (76). Finally, there have been some reports of abuse, dependence, and withdrawal associated with zolpidem, particularly in individuals with a history of drug or alcohol abuse (122). There are no randomized, controlled trials of zolpidem or zaleplon of greater than 5 weeks (75,81,82); therefore, few conclusions can be drawn about their efficacy and safety in the longer term, although open-label studies have not demonstrated significant safety concerns with longer-term use (123,124).

**Trazodone**

There is evidence that use of antidepressants for insomnia is increasing due to physician perceptions of their better safety profiles over those of hypnotics, absence of longer-term safety and efficacy data for hypnotics, and FDA prescribing restrictions for benzodiazepines. Data compiled for 1987–1996 (63) concerning the use of medications for insomnia demonstrated a reduction in hypnotic mentions by 53.7%, whereas use of antidepressants (apparently sedating antidepressants) increased by 146% (63).

Trazodone is currently the second most commonly prescribed agent for insomnia (125), despite the paucity of data evaluating its effectiveness in the treatment of insomnia independent of depression. Since 1980, fewer than 100 patients treated with trazodone have been assessed objectively in sleep laboratory studies. The largest subjective sleep studies (126–129) and many of the objective sleep studies (73,130,131) of trazodone have been conducted in depressed patients, not primary insomniacs, in many instances with doses 2 to 4 times higher than those used in insomnia. However, in the one placebo-controlled, double-blind study of primary insomniacs, trazodone 50 mg was effective in improving sleep latency and measures of sleep maintenance (71), though zolpidem was more effective than trazodone in the former, but not the latter measure. No trazodone trials have exceeded 6 weeks of active treatment, and many of those studies of 2 to 4 weeks’ duration have demonstrated evidence of tolerance on some measures (71,130–132). Side effects (133) and drug-drug interactions (134) may be problematic with trazodone use. Dizziness and sedation, dry mouth, headache, and hypotension are known adverse effects of trazodone, though these are less common in the doses commonly used for sleep (50–100 mg) than those used for the treatment of depression (133). Priapism is also a rare side effect of trazodone. Data submitted to the FDA indicated that the majority of cases occurred with doses of between 50 and 150 mg/day (135). Finally, several case reports suggest that cardiac toxicity can occur with trazodone in patients with pre-existing heart disease (136).

**Other Agents Used as Hypnotics**

Sedating agents used for a variety of indications in psychiatry and neurology are also being used as second- or third-line...
hypotheses when benzodiazepine or non-benzodiazepine hypnотics are contraindicated or have failed. These include gabapentin (137), quietapine (138), olanzapine (139), and gabapentin (140). A number of these agents appear to increase the percentage of slow wave sleep observed on overnight polysomnography (141, 142). However, the functional significance of this change in sleep architecture remains to be determined. Similarly, these agents may produce next day sedation or metabolic abnormalities.

**Progress in Insomnia Therapy**

Chronic insomnia has a high prevalence and significant social and economic impact, yet remains undertreated. This undertreatment may be related to (a) the lack of understanding of the longer-term consequences of insomnia, (b) the dearth of existing evidence for efficacy and safety of hypnotic agents beyond a few weeks of treatment, and (c) their lack of efficacy in treating sleep maintenance symptoms without resultant next-day side effects.

Other agents are under development to treat insomnia. One of these agents, eszopiclone, was well tolerated in a study of efficacy and safety over 6 months of double-blind use. Eszopiclone is a non-benzodiazepine (cyclopyrrole) agent (143), with a time to peak concentration of 1 hour and a half-life of 5.6 hours (144,145). Compared with placebo, eszopiclone 3.0 mg was found to significantly reduce the time to sleep onset, increase total sleep time, and reduce WASO and number of awakenings by self-report. Subjective reports of next-day benefit included improved alertness, daytime ability to function, and sense of physical well-being. Importantly, there was no evidence of reduction in benefit over 6 months of nightly use (146). Another non-benzodiazepine, indiplon, with a 1.5-hour half-life, in a modified release form that extends its duration of action, has been found to significantly reduce the time to sleep onset, increase total sleep time, and reduce WASO and number of awakenings by self-report.

**CONCLUSION**

Insomnia is a common symptom in psychiatric patients. Existing data suggests that insomnia is associated with both acute psychological and professional dysfunction, as well as an increased incidence of psychiatric illness. Physicians should assess not only the risks of treatment, but of the lack of treatment of insomnia. Short-term use of benzodiazepine and non-benzodiazepine hypnotics for insomnia in those with insomnia-related dysfunction is encouraged. Newer agents, with demonstrated efficacy for chronic treatment of insomnia, may soon be available, and allow for treatment of this often-chronic symptom.

**ACKNOWLEDGMENTS**

The authors would like to acknowledge Sepracor Inc. for its assistance in the preparation of this manuscript.

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