Pharmacologic Management of Insomnia

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Pharmacotherapy is indicated for many types of insomnia, most notably transient insomnia associated with stress, acute illness, or jet lag. Many patients with chronic insomnia, including primary insomnia and insomnia secondary to a variety of medical and psychiatric disorders, also benefit from pharmacotherapy. Relatively few individuals receive prescription medication to help them sleep, and the majority use medication for a few nights to several weeks, as opposed to continuous use for months or years. The hypnotics available on the U.S. market today are benzodiazepine receptor agonists (BZRAs). The BZRAs are efficacious in reducing sleep latency, increasing total sleep time, reducing awakenings, and improving sleep quality without the development of tolerance in studies as long as 6 months. Side effects of the BZRAs are infrequent, dose-related, and related to the sedative properties of the drug. Sedating antidepressants are also frequently prescribed to promote sleep despite inadequate data to support their efficacy for this indication and a greater potential for clinically troublesome side effects. *(J Clin Psychiatry 2004;65[suppl 16]:41–45)*

Two decades ago, a consensus statement[1] on the use of medications to promote sleep indicated that benzodiazepine hypnotics were the preferred drugs and that the lowest effective dose should be used for the shortest period of time judged to be clinically necessary. Pharmacotherapy was acknowledged as an appropriate choice for transient and short-term insomnia (i.e., 4 weeks or less), and use of a short- or intermediate-acting drug was recommended unless there was a need for daytime anxiolysis, in which case long-acting drugs might be appropriate. Regarding chronic insomnia, controversy existed over the appropriateness of pharmacotherapy, and the consensus document stated only that "a short trial (less than 1 month) of sleep-promoting medication concomitant with behavioral treatment may also be indicated."[1(p2411)] The viewpoint at that time was that hypnotics were not a first-line treatment for chronic insomnia because insomnia was considered a symptom of a medical, psychiatric, or behavioral condition that would remit with treatment of the underlying condition. Nevertheless, long-term use of hypnotics has not been uncommon in the past 2 decades. Approximately 20% of hypnotic users in the United States report nightly use of hypnotics for a period of 4 months or more.[2]

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This article is derived from the teleconference "Differential Diagnosis and Management of Daytime Sleepiness and Nighttime Wakefulness," which was held April 5, 7, and 22, 2004, and supported by an unrestricted educational grant from Cephalon, Inc.

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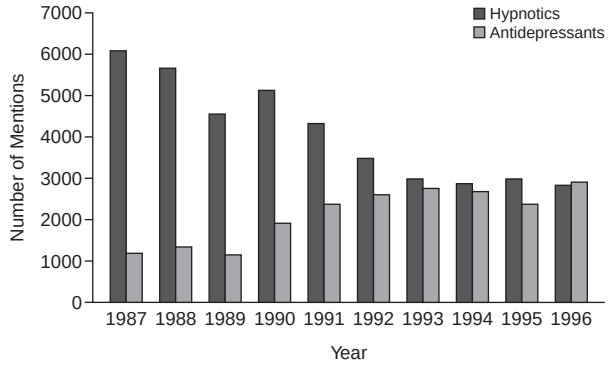
There continues to be widespread agreement that hypnotics are an appropriate therapy for transient and short-term insomnia. In recent years, a number of advances in our understanding of chronic insomnia, its relation to psychiatric and medical conditions, and the continued development of hypnotic drugs have led many clinicians and investigators to reevaluate pharmacotherapy for chronic insomnia.[3] Considerable evidence indicates that a substantial minority of chronic insomniacs have a primary condition without a precipitating psychiatric, medical, or behavioral illness.[4,5] Even when insomnia coexists with other medical and psychiatric conditions, the degree of sleep disturbance contributes significantly to overall clinical status. Insomnia is a major risk factor for mood disorders, even a number of years subsequent to the insomnia,[6,7] and there are suggestions that improved sleep may be associated with a more rapid antidepressant response[8] and reduced suicide risk.[9,10] Growing evidence suggests that even when underlying conditions are treated, insomnia does not always remit.[11] In recognizing these changes, sleep medicine specialists have begun to reconsider the situations in which long-term use of hypnotics would be appropriate.[3,12,13] Although no consensus has yet been reached, the efficacy and safety profile of available hypnotics is sufficiently positive that, in the absence of dose escalation, there appears to be no medical or scientific reason to withdraw or withhold long-term pharmacotherapy from a patient with chronic insomnia.

Interestingly, as thought on pharmacotherapy was evolving, a shift toward less pharmacologic treatment of insomnia occurred.[14] From 1987 to 1996, the frequency of pharmacologic treatment of insomnia declined by 24% (Figure 1). Also, while use of hypnotics declined by 54%, use of antidepressants for the treatment of insomnia increased by 146% (see Figure 1).

Figure 1. Number of Drug Mentions in the National Disease and Therapeutic Index for Hypnotic Medications and Antidepressant Medications in the Treatment of Insomnia[a]



[a]Data from Walsh and Schweitzer.[14]

The hypnotics available in the United States today are benzodiazepine receptor agonists (BZRAs). Five of these are chemically benzodiazepines; the other 2, zolpidem and zaleplon, are not benzodiazepines but act at benzodiazepine receptor sites. Sedating antidepressants are also used frequently to treat insomnia despite the availability of minimal data to support this practice. Below is a brief review of the efficacy and safety data for BZRAs and sedating antidepressants for the treatment of insomnia.

BENZODIAZEPINE RECEPTOR AGONISTS IN THE TREATMENT OF INSOMNIA

Meta-analyses[15,16] of published reports on BZRAs have concluded that they are efficacious in reducing sleep latency, increasing total sleep time, reducing the number of awakenings overnight, and improving sleep quality. However, in the majority of studies included in these meta-analyses, the medications were administered for less than 2 weeks. Because of the growing interest in the treatment of chronic insomnia, some of the longer-duration studies of hypnotics are highlighted below.

Efficacy in Multiple-Week Studies

Two early studies[17,18] without parallel placebo groups suggested hypnotic efficacy for several weeks. Lamphere et al.[17] administered estazolam, 2 mg nightly, for 6 weeks. Sleep latency, total sleep time, and sleep efficiency all improved significantly from baseline with estazolam treatment, and these gains were maintained throughout the treatment period. No signs of tolerance or rebound insomnia were evident. In another study,[18] triazolam, 0.5 mg, consistently reduced sleep latency when given nightly for 6 weeks, without significant problems upon drug discontinuation.

Zaleplon and zolpidem are BZRAs that bind more selectively to one subtype of benzodiazepine receptor. It has been hypothesized that this selectivity may lead to better side effect profiles for these 2 agents than for the benzodiazepines, although this hypothesis has not been definitively demonstrated. The primary hypnotic effect of zaleplon is to reduce sleep latency. It is a short-acting drug, and it does not significantly increase total sleep time. Zolpidem has a longer duration of action and both reduces sleep latency and increases total sleep time.

A double-blind, placebo-controlled 5-week trial[19] of zaleplon, 10 mg nightly, in primary insomnia found that sleep latency was significantly decreased compared with placebo throughout the study. Additionally, although no statistical significance was found, total sleep time showed a numerical improvement with zaleplon. Discontinuation effects were not significantly different between the 2 groups.

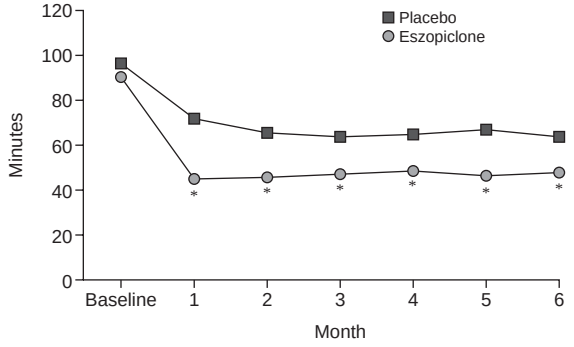
Scharf et al.[20] performed a double-blind, placebo-controlled investigation of zolpidem, 10 and 15 mg, for the treatment of chronic insomnia. Both doses of zolpidem produced significantly shorter sleep latencies and significantly higher sleep efficiency throughout the 5 weeks of the study.

The treatment of insomnia over long periods of time does not necessarily mean that medication must be taken every night. For example, non-nightly use of zolpidem, 10 mg, versus placebo has been investigated for 8 weeks in primary insomnia.[21] Patients were instructed to take a pill (which was either a dose of zolpidem or a placebo pill) at night when they felt they needed it, with the restriction that they must take a pill at least 3 nights and no more than 5 nights each week. On the nights they took a pill, the patients taking zolpidem had a significantly shorter sleep latency, longer total sleep time, lower number of awakenings, and better sleep quality ($p < .007$) compared with the patients taking placebo. Importantly, the number of pills taken by the zolpidem group did not exceed those taken by the placebo group, and pill-taking remained stable across study weeks for both groups. Further, a careful analysis of nights without a pill showed no evidence of rebound insomnia.

Efficacy in a Multiple-Month Study

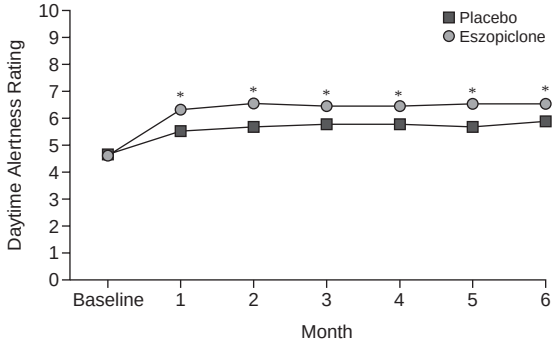
The first truly long-term efficacy trial[22] for a BZRA was published in 2003. In a randomized, double-blind, placebo-controlled trial, eszopiclone, 3 mg (which is under review for approval by the U.S. Food and Drug Administration), was administered nightly for 6 months. Patients with primary insomnia treated with eszopiclone reported significantly improved sleep latency (Figure 2), increased total sleep time, decreased time awake after sleep onset, and improved sleep quality compared with the patients given placebo. These improvements were maintained throughout the 6 months of the study, with multiple statistical analyses demonstrating an absence of tolerance. Eszopiclone has an intermediate duration of action, which

Figure 2. Sleep Latency of Patients Given 3 mg of Eszopiclone and Patients Given Placebo[a]



[a]Data from Krystal et al.[22]
*p < .0001.

Figure 3. Patients' Ratings on a 1 to 10 Scale of Daytime Alertness While Taking Eszopiclone or Placebo[a]



[a]Data from Krystal et al.[22]
*p < .0001.

might lead to concern about residual sedation in the morning. However, in this 6-month study,[22] the patients given eszopiclone rated their daytime alertness (Figure 3) and ability to function as significantly better than did those given placebo. Finally, similar rates of adverse events were reported after medication discontinuation in the group given placebo and in the group given eszopiclone for 6 months.

Efficacy in Insomnia With Comorbid Conditions

Although BZRAs are used clinically in patients of all types, not just primary insomniacs, relatively few studies have been published of insomnia in medically or psychiatrically ill patients. Those published do, however, indicate that BZRAs have similar effects on sleep regardless if the study population has primary insomnia or other forms of sleep disruption. In a 4-week study[23] of zolpidem, 10 mg, for persistent insomnia in patients with depression currently treated with selective serotonin reuptake inhibitors (SSRIs), zolpidem significantly increased total sleep time and improved sleep quality compared with placebo throughout the duration of the study. Patients given zolpidem also improved significantly more on daytime functioning measures during weeks 2 through 4 than did the patients given placebo ($p < .05$). On the first night following discontinuation of treatment with zolpidem, patients reported lower total sleep time and quality of sleep than at baseline, but by the second night they experienced fewer awakenings than those who took placebo. No evidence of a withdrawal reaction was reported.

Patients with chronic pain conditions and other medical illnesses often suffer from sleep disturbances and may benefit significantly from hypnotic therapy. A crossover study[24] of triazolam (nighttime dose clinically titrated from 0.125 to 0.5 mg) versus placebo in the treatment of insomnia in patients with rheumatoid arthritis found significantly improved sleep latency, total sleep time, and number of awakenings. As importantly, objectively assessed daytime alertness improved and the duration of morning stiffness was significantly shortened after triazolam treatment.

Side Effects

The most common side effects of BZRAs are drowsiness, dizziness, and headache. Much less often more serious side effects, such as cognitive impairment, can occur. The side effects of the BZRAs are highly dose dependent. Therefore, it is important to prescribe the lowest effective dose.

As mentioned earlier, one occasional side effect of BZRA usage is rebound insomnia. On the first night following abrupt discontinuation of a short-acting hypnotic, sleep may be worse than it was prior to treatment. In the clinical situation, it is difficult to determine if sleep has become worse than prior to treatment or if the original sleep difficulty has simply returned with treatment cessation. If rebound insomnia is suspected, the patient should be told that research clearly shows that it lasts only 1 or 2 nights. Rebound insomnia can be avoided by tapering the dose over a few nights when the medication is discontinued. If a patient takes a BZRA a few nights of the week and does not take it on others, sleep quality usually does not deteriorate so greatly on the nights that the medication is not taken that the patient increases frequency of use.

BZRAs with a long duration of action can cause residual daytime sedation in some patients. This sedation can usually be lessened by using a shorter-acting medication. If a patient is particularly anxious or hyperaroused during the day, a long-acting medication may not be particularly problematic, but some patients may not be able to tolerate the sedation and may be at risk (e.g., when driving).

In one study,[25] individuals with insomnia were asked to take into account all the positive and negative effects of

the medication they were taking for their sleep problem and decide whether they would take that medication again for the same purpose. Of the patients taking one or more BZRA, between 74% and 84% said they would, while 61% of patients taking over-the-counter medications agreed.

SEDATING ANTIDEPRESSANTS IN THE TREATMENT OF INSOMNIA

Although the BZRAs have been well studied, less is known about the efficacy and safety of sedating antidepressants (e.g., trazodone, amitriptyline, doxepin, and mirtazapine) for the treatment of insomnia. Most information on the sedative properties of these antidepressants comes from experience with depressed individuals; a dearth of information exists about the efficacy and safety of these agents in the treatment of insomnia that is not associated with depression.[3]

One study[26] has compared trazodone, 50 mg, to zolpidem, 10 mg, for treatment of primary insomnia. During the first week of study, both trazodone and zolpidem produced shorter sleep latencies than placebo, but zolpidem reduced sleep latency more than trazodone. In the second week, zolpidem continued to reduce sleep latency, but there was no difference in sleep latency between trazodone and placebo. The 2 drugs had similar effects on total sleep time in this investigation.

Tricyclic antidepressants (TCAs) and other sedating antidepressants have more frequent and generally more problematic side effect profiles compared with BZRAs. In fact, SSRIs have largely supplanted TCAs and other sedating antidepressants for the treatment of depression because of superior tolerability and safety.[27] The lethal-dose/effective-dose margin is much narrower with antidepressants than BZRAs. The elimination rate for most sedating antidepressants is generally slow, with mean half-lives of about 9 to 30 hours, exclusive of any active metabolites. Thus, although residual sedation has not been assessed for these drugs, the pharmacokinetics would indicate that morning carryover is likely.

Two studies[28,29] of sedating antidepressants in primary insomniacs support the position that sedating antidepressants used in this context have more frequent and more serious safety concerns than do BZRAs. In one investigation,[28] 2 of 4 primary insomnia patients who discontinued doxepin treatment had significant adverse events, specifically leukopenia, thrombopenia, and increased levels of liver enzymes. In a direct comparison of lormetazepam and trimipramine in primary insomniacs,[29] dizziness, dry mouth, headache, and nausea were more frequent, and severe side effects were twice as common with trimipramine than with lormetazepam. Mirtazapine is associated with weight gain and increased appetite, as well as high rates of daytime somnolence and dizziness.[30]

Trazodone may be viewed as safe to use as a hypnotic because of the many reports in the 1980s and 1990s that it was safer and caused fewer side effects than did TCAs. However, these studies predate the availability of SSRIs and the comparison of trazodone to SSRIs would probably be less favorable. Orthostatic hypotension, weakness, and light-headedness are not uncommon.[31] A number of cases of cardiac conduction abnormalities, hypotension, and other cardiovascular concerns have been reported to be associated with trazodone use by patients with preexisting heart disease.[32–35] Priapism is an infrequent but potentially serious side effect even with low daily doses of trazodone.[36,37]

In sum, the use of sedating antidepressants rather than BZRAs for treatment of insomnia based upon overall safety or efficacy profiles is not supported by available information. Substance abuse patients may be one type of patient for whom sedating antidepressants may have a more favorable risk-benefit ratio.

FUTURE DIRECTIONS

A number of medications are currently in development for the treatment of insomnia. The mechanisms of action for some of these drugs is different from agonism at the benzodiazepine receptor. Drugs in development include direct γ-aminobutyric acid (GABA) agonists, GABA reuptake inhibitors, corticotropin-releasing hormone antagonists, and serotonin-2 antagonists. The pharmacotherapy of insomnia may be substantially different in upcoming years.

Drug names: amitriptyline (Elavil and others), doxepin (Sinequan and others), estazolam (Prosom and others), mirtazapine (Remeron and others), trazodone (Desyrel and others), triazolam (Halcion and others), trimipramine (Surmontil), zaleplon (Sonata), zolpidem (Ambien).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, amitriptyline, doxepin, mirtazapine, trazodone, trimipramine, eszopiclone, and lormetazepam are not approved by the U.S. Food and Drug Administration for the treatment of insomnia.

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