In the originally published article, an incorrect version of Table 1 was printed. The corrected Table 1 appears on page 7, the resulting corrected reference citations in text appear on page 6, and additional references 20–23 in the reference list appear on page 8.

Trends in the Pharmacologic Management of Insomnia

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A variety of methods have been used to treat insomnia over the years. Alcohol, opium, and herbs were replaced by barbiturates early in the 20th century. In the 1960s, barbiturates were replaced with a safer class of medication, the benzodiazepines. Later, the selective benzodiazepine receptor agonists (BZRAs), agents that work through the benzodiazepine receptor but are not chemically benzodiazepines, were developed. These medications have proved to be safer, less toxic, and just as effective without the heightened risk of dependence compared with their predecessors. Several over-the-counter medications, including antihistamines, herbal supplements, valerian, melatonin, and L-tryptophan, are popular sleep aids, but little evidence supports their use for insomnia. Despite the lack of U.S. Food and Drug Administration (FDA) approval for insomnia, the risk of adverse events, and limited efficacy, antidepressants remain popular treatments for sleep disorders. Recent FDA approvals of 2 longer acting selective BZRAs have been unique in their lack of limitation to short-term usage as well as their indication for sleep maintenance. In late 2005, the melatonin receptor agonist ramelteon was approved for sleep initiation and is likewise not restricted to short-term use. New compounds under development include indiplon, another selective BZRA, and gaboxadol, a selective extrasynaptic γ-aminobutyric acid-A agonist. Additional melatonin receptor agonists and medications that work through the serotonin system are under development. Physician education is an important component to ensuring that patients receive safe and adequate treatment for their insomnia.

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People have been suffering from insomnia as long as humans have been on the Earth, and for nearly as long, they have used agents such as alcohol, opium, and herbs for the promotion of sleep. In the early 20th century, medications such as the barbiturates were widely used for the promotion of sleep, but these medications put patients at risk for overdose because of their low therapeutic indices and for withdrawal symptoms when discontinued. In the 1960s a new class of compounds, the benzodiazepines, was developed. The benzodiazepines were an improvement in safety over the barbiturates but still carried some concerns about dependence. In the 1980s, agents that work through the benzodiazepine receptor, but are not benzodiazepines chemically, were introduced. These are known as the selective benzodiazepine receptor agonists (BZRAs). In 2005, a new hypnotic medication was approved that works through the melatonin receptor agonist system. These newer hypnotics (the selective BZRAs and the melatonin receptor agonist) are safer, less toxic, and less likely to lead to abuse and dependence than the older medications, while still being effective.

Although several effective medications are currently approved for insomnia, physicians still recommend many nonapproved medications. These primarily include over-the-counter antihistamines and off-label use of antidepressants, often in nondepressed patients with insomnia. Walsh and Schweitzer[1] gathered data on trends in the use of medications to promote sleep from 1987 to 1996. The total number of hypnotic medication prescriptions dropped from about 1987 onward (Figure 1). While the use of hypnotic medications was decreasing, likely due to growing concerns over abuse and long-term usage safety, the use of antidepressants for the treatment of insomnia was increasing.

CURRENT STATE OF PHARMACOLOGIC MANAGEMENT OF INSOMNIA

The National Institutes of Health (NIH) held a consensus development conference in 2005 to discuss the state of insomnia research and treatment and to identify research needs. The NIH consensus development conference panel issued a statement[2] that examined each class of medication used by individuals with insomnia and evaluated their benefits.

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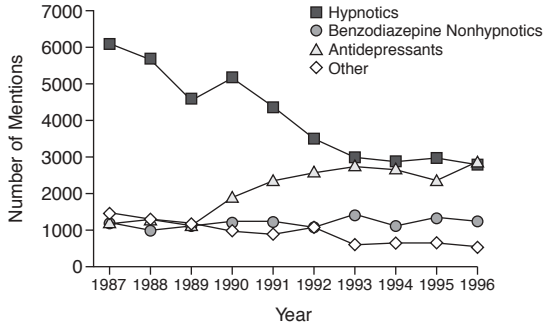
Figure 1. Number of Drug Mentions in the National Disease and Therapeutic Index for Medications for the Treatment of Insomnia[a]



[a]Data from Walsh and Schweitzer.[1]

Over-the-Counter Medications

The NIH conference panel[2] reviewed the use of over-the-counter agents for the treatment of insomnia. Antihistamines such as diphenhydramine are commonly used by individuals to promote sleep, but there is little evidence supporting their use, and they are associated with side effects such as residual sedation. Herbal supplements, valerian, melatonin, and L-tryptophan are also used by individuals to aid in sleep, but again the data supporting their use are limited. Moreover, the potential purity of these compounds that consumers buy is a concern because they are not regulated as medications. Valerian and L-tryptophan may also cause toxicity in high doses.

Alcohol is widely used by patients to remedy their insomnia. Even though alcohol may aid in sleep initiation, it is ineffective at increasing quality of sleep, thus often leading to complaints of next day residual unwanted effects. Further, patients who are using alcohol tend to develop tolerance and increase their consumption. Finally, alcohol works like a compound with a short half-life in that it will initially promote sleep but will cause withdrawal symptoms when the individual discontinues use.

Prescription Medications Not Approved by the U.S. Food and Drug Administration (FDA)

The NIH conference panel[2] also discussed the issue of the compounds that are frequently used for the promotion of sleep but are not approved by the FDA for the treatment of insomnia, such as antidepressants, especially the older tricyclic antidepressants (TCAs). Many physicians believe that these antidepressants are safe, but the conference panel raised concerns about adverse effects that develop during treatment and limit the efficacy of these medications. Curiously, in the treatment of depression, most physicians have replaced nearly all antidepressant use from TCAs to selective serotonin reuptake inhibitors not due to better efficacy, but because of concerns over safety and side effects. Yet, these very medications are used more commonly to treat insomnia than currently approved agents.

Trazodone, in particular, is the most commonly prescribed medication in the United States for sleep problems, but it is not approved for insomnia.[2] No research has been performed to indicate the therapeutic dose of this medication, and there are limited data supporting its efficacy for sleep. Walsh et al.[3] examined the effectiveness of treatment with trazodone 50 mg/day for 14 days in patients with primary insomnia. Even though initially there was modest improvement in some sleep parameters, at the end of the 14-day period, there was no significant difference in sleep latency between the patients who took trazodone and the patients who took placebo. Trazodone also carries with it concerns about serious side effects, such as orthostatic hypotension (and an increased risk of falls) and priapism, as well as a black-box warning of antidepressants increasing suicidality in short-term studies in children and adolescents with depression.[2]

Antipsychotic medications are increasing in popularity as off-label treatments for sleep, but they are associated with side effects such as weight gain, diabetes, and tardive dyskinesia.[2] Also, black-box warnings have recently been added to all atypical antipsychotics regarding usage in elderly patients due to increased risk of death.

Prescription Medications Approved by the FDA

The benzodiazepines, such as estazolam, flurazepam, and quazepam, were the primary medications prescribed for sleep promotion for years. However, physicians had concerns about long-term use and the possibility of dependency. When the selective BZRAs were introduced, they were welcomed because they were more selective in their action and did not raise as many concerns about side effects, but still were only indicated for short-term use. Recently, the FDA approved medications for sleep with no restriction on long-term use. These medications include the selective BZRAs zolpidem extended-release and eszopiclone and the melatonin receptor agonist ramelteon.

Although short-term and medium-term data are available on medications approved for insomnia, more long-term data on these medications are needed, especially showing daytime improvement and long-term benefit.[2] Ideally, these data would come from trials that lasted longer than a year. A most important end point in long-term effect should be treatment benefit on outcome; that is, it should be shown whether insomnia treatment not only improves sleep parameters, but also improves the comorbid condition. See Table 1 for an overview of the available data on medications approved for the treatment of insomnia.[4–13,16,20–23]

Nonbenzodiazepine hypnotics. In a 12-week study by Perlis et al.,[10] 199 patients with primary insomnia were

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Table 1. Comparisons of Medications Approved for the Treatment of Insomnia[a]

	Zaleplon	Zolpidem	Zolpidem Extended-Release	Eszopiclone	Ramelteon
Receptor selectivity	BZ_1[4]	BZ_1[5]	BZ_1[6]	BZ_1 and BZ_2[7]	MT_1 and MT_2[8]
Dosage (mg)	5, 10[4]	5, 10[5]	6.25, 12.5[6]	1, 2, 3[7]	8[8]
Schedule	IV[4]	IV[5]	IV[6]	IV[7]	Not scheduled[8]
Restricted to short-term usage	Yes[4]	Yes[5]	No[6]	No[7]	No[8]
Sleep latency	↓[4]	↓[5]	↓[6]	↓[7]	↓[8]
Number of awakenings	…[20–22]	↓[5]	↓[11]	↓[12]	…[16]
Wake after sleep onset	…[b]	…[10,23]	↓[6]	↓[7]	…[13]
Total sleep time	↑[9]	↑[5]	↑[11]	↑[7]	↑[13]

[a]Data from Sonata [prescribing information],[4] Ambien [prescribing information],[5] Ambien CR [prescribing information],[6] Lunesta [prescribing information],[7] Rozerem [prescribing information],[8] Ancoli-Israel et al.,[9] Perlis et al.,[10] Erman et al.,[11] Halas,[12] Erman et al.,[13] Roth et al.,[16] Elie et al.,[20] Ancoli-Israel et al.,[21] Hedner et al.,[22] and Scharf et al.[23]
[b]Zaleplon is known to have no effect on wake after sleep onset because of its short half-life.
Symbols: ↑ = increased, ↓ = decreased, … = no consistent effect.
Abbreviations: BZ = benzodiazepine, MT = melatonin.

randomly assigned to take immediate-release zolpidem, 10 mg/day, or placebo as needed 3 to 5 nights a week. On the nights they took a pill, the patients taking zolpidem reported a significantly shorter sleep latency than the patients given placebo.

Recently, Erman et al.[11] announced the results of a 25-week multicenter, double-blind, placebo-controlled study of zolpidem extended-release in adults with chronic insomnia. Participants took either zolpidem extended-release or placebo as needed for 3 to 7 nights each week of the study. Zolpidem extended-release significantly improved sleep onset latency ($p = .0014$) with no tolerance observed and no worsening of total sleep time or wake after sleep onset reported after medication discontinuation.

Zaleplon has been studied in patients for up to a year. In a report of open-label extensions of 2 clinical trials, Ancoli-Israel et al.[9] gave patients aged 65 to 86 years 5 mg/day of zaleplon for 6 to 12 months. Patients reported significantly ($p < .001$) reduced time to sleep onset overall and on their last measurement in the study. No significant rebound insomnia was found.

Eszopiclone was studied for 6 months[14] and 12 months[15] in patients with chronic insomnia. In the 6-month study, Krystal et al.[14] randomly assigned 788 study participants to receive either 3 mg/day of eszopiclone or placebo. The patients taking eszopiclone reported a significantly ($p < .0001$) lower sleep latency than those given placebo. This difference was evident through all 6 months of the study.

Melatonin receptor agonist. Ramelteon, the only melatonin receptor agonist currently available, was approved by the FDA in 2005. Ramelteon is different from native melatonin in that it is not a hormone. It is also unlike any medications that have been approved for sleep promotion to date. The benzodiazepines and nonbenzodiazepine hypnotics are benzodiazepine receptor agonists, meaning that they work with benzodiazepine receptors on the γ-aminobutyric acid-A ($GABA_A$) receptor. Ramelteon acts on the melatonin (MT) receptors MT_1 and MT_2, which are found primarily in the suprachiasmatic nucleus, which controls the body's "sleep clock." Ramelteon is indicated for sleep initiation and is not restricted to short-term use.

Roth et al.[16] conducted a 5-week, double-blind study of ramelteon in adults ≥ 65 years of age. Participants ($N = 829$) were randomly assigned to receive 4 mg/day or 8 mg/day of ramelteon or placebo. Both doses of ramelteon significantly reduced sleep latency at week 1 ($p = .008$) and week 5 ($p = .028$ for 4 mg/day, $p < .001$ for 8 mg/day). No evidence of rebound insomnia or withdrawal symptoms was seen. Ramelteon is currently approved for use at the 8-mg dosage only.

EMERGING PHARMACOLOGIC THERAPIES

New compounds are in development for the treatment of insomnia. One of these, indiplon, is another selective BZRA. Two formulations of indiplon are in clinical development, an immediate-release form, similar to zaleplon in its half-life and duration of action, and a modified-release form, with a longer half-life and duration of action. With this medication as with other modified-release formulations, physicians may have a treatment option that has a rapid onset, a sustained effect, and then a rapid fall-off.

The results of a 4-week study[17] of indiplon were presented at the 2006 American Psychiatric Association annual meeting. In a double-blind, randomized trial, 248 patients with insomnia were given 15 mg/day of indiplon or placebo. Total sleep time, the primary measure, was rated subjectively by participants. Patients given indiplon reported significantly greater improvement in total sleep time than those given placebo ($p < .001$).

Another compound that is approaching FDA approval is gaboxadol. Gaboxadol, a selective extrasynaptic $GABA_A$ agonist, works through the same $GABA_A$ receptor complex as the benzodiazepine receptor agonists, but it does not work at the benzodiazepine receptor site. Because its action takes place at different receptor sites, gaboxadol is thought to have different properties from the benzodiazepine receptor agonists. It appears to promote slow wave sleep, which may lead to a perception of deeper

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sleep during the night without negative effects on rapid eye movement sleep.[18,19]

Other compounds that are being developed for insomnia include additional melatonin receptor agonists, similar to ramelteon, and medications that work through the serotonin system. These medications have entirely different mechanisms of action from the benzodiazepine receptor agonists, and they may prompt a shift in the future about what works to promote sleep. The result of these new developments will be that physicians will have a broader range of agents available to treat sleep problems.

CONCLUSION

With more information emerging about insomnia as well as more medications available for the treatment of insomnia, there is a growing need for more education so that physicians may be better able to identify and treat sleep problems. The NIH and other bodies in the medical establishment are starting to take a closer look at issues with medications for the treatment of insomnia. Practicing physicians need to be given a better understanding of the impact of insomnia on functioning in everyday life and how these medications work to lessen that impact.

Drug names: diphenhydramine (Benadryl and others), estazolam (Prosom and others), eszopiclone (Lunesta), flurazepam (Dalmane and others), quazepam (Doral), ramelteon (Rozerem), trazodone (Desyrel and others), zaleplon (Sonata), zolpidem (Ambien), zolpidem extended-release (Ambien CR).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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