Therapeutic Options in the Treatment of Insomnia

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Pharmacologic and nonpharmacologic therapies both have roles in the treatment of insomnia. The benzodiazepines, when first introduced, were a major improvement over earlier treatments for insomnia in terms of their safety and efficacy. Since then, the nonbenzodiazepine benzodiazepine receptor agonists have been developed, which have provided advantages over the older medications and are currently first-line medication treatment for insomnia. Although antidepressants, antipsychotics, and anticonvulsants are often prescribed for the treatment of insomnia, they are not approved by the U.S. Food and Drug Administration for this indication and have side effects that are sometimes severe. New types of medications that have different modes of action from the benzodiazepine receptor agonists are now being developed, and one, a selective melatonin receptor agonist, has recently been approved for treatment of insomnia. Nonpharmacologic therapies can also help patients learn how to fall asleep faster and improve sleep quality. It is important for physicians to teach patients good sleep hygiene as part of their treatment. Cognitive-behavioral therapy is effective in the treatment of insomnia, alone and in combination with pharmacotherapy, but finding a qualified provider can be difficult and the patient must be willing to take the time to learn the therapies and wait for them to show effect.

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Individuals have different levels of predisposition to insomnia. Some people may normally be "near-insomniacs," with increased risk of developing insomnia. This vulnerability can trigger a frank sleep disorder as a consequence of stress, such as job troubles, family problems, or illness. Other people who normally have no trouble sleeping may experience insomnia secondary to exposure to precipitating events severe enough to disrupt their natural tendencies toward regular sleep. It is the physician's role to try to mitigate the factors that promote insomnia and to treat the effects of insomnia when it occurs. This can be done with both pharmacotherapy and psychotherapy.

In an ideal world, no one would need medication for sleep. In the real world in which we live, pharmacotherapy is the most common treatment for insomnia. Although we live in a world in which medications are often required, we can help patients learn techniques that allow them to sleep more easily without excessive reliance on pharmacologic agents. Education and behavioral therapies that promote good sleep hygiene should be part of every patient's treatment. A problem with behavioral therapy, however, is that it takes time to learn and time to show its effects; because of this necessary delay, pharmacotherapy has an advantage in patients who are in need of immediate aid or are unable to take the time to learn and practice behavioral therapies.

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PHARMACOTHERAPY

Throughout history, people have used medications to promote sleep. Opium and alcohol were both used to promote sleep in ancient times, and there are references to the use of various herbs for this purpose in the Bible and in Shakespeare's works. In the 1800s, morphine, potassium bromide, and chloral hydrate were used to promote sleep, and in the early 20th century, the barbiturates were introduced. All of these medications, although effective in inducing sleep, put patients at a risk for development of tolerance, experiencing withdrawal effects, or suffering a fatal overdose. The modern era of pharmacology of sleep began in the 1950s and 1960s with the introduction of medications for sleep promoted as being safer than the barbiturates, including glutethimide and methaqualone. However, over time, these medications demonstrated their own potentials for tolerance, abuse, and overdosage.

Benzodiazepine Receptor Agonists

In 1960, the first benzodiazepine anxiolytic compound, chlordiazepoxide, was introduced with the brand name "Librium." Other benzodiazepine anxiolytics followed, most famously diazepam (Valium), introduced in 1963. Flurazepam (Dalmane), the first benzodiazepine specifically marketed as a hypnotic agent, was introduced in 1970. In the 1980s, compounds such as zopiclone and zolpidem with agonist effects at the benzodiazepine receptor

but without a benzodiazepine chemical structure were introduced. The benzodiazepine receptor agonists are different from older compounds such as barbiturates in several ways. The older compounds have diffuse sedative effects within the brain, including suppressant effects on centers controlling ventilatory drive. They also bind to barbiturate or other receptor sites on the γ-aminobutyric acid-A (GABA-A) complex in the brain, with inhibitory effects on arousal and alertness.

All benzodiazepine receptor agonists bind to benzodiazepine receptors, but in several different fashions: the benzodiazepines typically bind to multiple benzodiazepine receptors in a nonselective fashion, and the nonbenzodiazepines may bind selectively to α_1 or α_3 receptors but not to α_2 benzodiazepine receptors.[1] The binding selectivity of the nonbenzodiazepine benzodiazepine receptor agonists means that they should not have the anxiolytic or muscle relaxant properties associated with the benzodiazepines and may also have fewer cognitive, memory, or motor effects than these agents.

Benzodiazepines. The benzodiazepines are effective in the promotion of sleep and are safer than the medications that preceded them, including the barbiturates and chloral hydrate. However, many of the benzodiazepines have long half-lives and a relatively long duration of action. This is a problem because when the therapeutic effect of a sleep-promoting medication spills over into the period when patients should be awake, promotion of sleep becomes a side effect. If the duration of action of a sleep-promoting medication is longer than the amount of time a patient has set aside for sleep, the effect will continue into daytime waking hours, and the patient will be at risk for residual sedation. Estazolam, flurazepam, and quazepam all have long half-lives and long duration of action, which gives them a relatively high probability of causing residual sedation. Temazepam, a compound with an intermediate half-life, has less of a risk of causing residual sedation, and triazolam, with a short half-life, has an even lower risk of causing residual sedation.

In addition to the risk for residual sedation, the benzodiazepines have other disadvantages. The benzodiazepines may cause side effects such as rebound insomnia and anterograde amnesia, and patients may experience withdrawal effects. Side effects may be dose-dependent, but these medications should still be prescribed with caution.

Nonbenzodiazepines. The nonbenzodiazepine benzodiazepine receptor agonists, which include zolpidem, zaleplon, and eszopiclone, provide effective and safe treatment for insomnia. They have short half-lives and short durations of action compared with most of the benzodiazepines and have a low probability of residual sedation. The nonbenzodiazepine benzodiazepine receptor agonists are schedule IV controlled substances, with a low abuse potential.

Although the initial focus of research on the nonbenzodiazepines was on their short-term effects on sleep initiation, newer data have been collected on their long-term benefits. Perlis et al.[2] looked at the effectiveness of zolpidem compared with placebo when given for 12 weeks. The subjects in this study (N = 199) were randomized to 2 groups, one receiving tablets containing 10 mg of zolpidem and the other receiving placebo tablets. They were instructed to take this sleep medication between 3 and 5 nights per week. The patients then recorded their observations in sleep diaries.

For the zolpidem group, on the nights that they took medication, subjects reported a significantly ($p \leq .05$) shorter sleep latency than those who took placebo. This difference in sleep latency was maintained through all 12 weeks of the study. On the nights that the participants did not take medication, there was no significant between-group difference with regard to reported sleep latency, suggesting that there was not a rebound effect.

Eszopiclone, which was approved in December 2004, is the newest of the nonbenzodiazepine benzodiazepine receptor agonists. It is the (S)-isomer of the medication zopiclone, which has been available outside the United States for many years. The effects of eszopiclone on sleep have been studied over a longer trial period than for zolpidem or zaleplon. In a 6-month double-blind trial,[3] 788 participants were randomly assigned to receive either 3 mg/day of eszopiclone or placebo. Sleep latency for the subjects taking eszopiclone was significantly lower ($p < .0001$) than for those taking placebo. This difference in sleep latency was sustained through all 6 months of the study, with no evidence of development of tolerance over the 6 months of the study.

Eszopiclone has a somewhat longer half-life and a longer duration of action than zolpidem and zaleplon. Because of this difference in duration of action, it would seem likely that patients taking eszopiclone will have a higher chance of experiencing residual sedation than those taking either zolpidem or zaleplon.

It is likely that as more studies are done, additional data will be generated to confirm the hypothesis that other nonbenzodiazepine benzodiazepine receptor agonists have the capacity to sustain their effects over long-term use. Extended-release formulas are also being developed to try to enhance the effectiveness of these agents with regard to sleep maintenance. With the new focus on use of benzodiazepine receptor agonists for long-term treatment, studies to assess the long-term efficacy of these extended-release formulations should be available in association with their release. A new nonbenzodiazepine benzodiazepine receptor agonist, indiplon, has been submitted for approval to the U.S. Food and Drug Administration (FDA). It is expected that, if it is approved, it will be produced in both immediate- and modified-release formulas. It is similar in half-life to zaleplon, but the planned modified-release formula will extend the duration of action of the medication in an attempt to improve sleep maintenance.

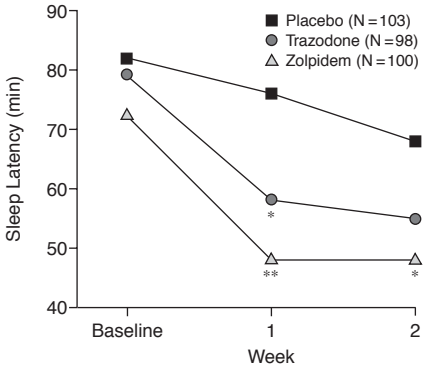
Antidepressants

Although the selective serotonin reuptake inhibitors (SSRIs), the tricyclic antidepressants (TCAs), and other antidepressants such as trazodone were not designed to treat insomnia, physicians often prescribe them for that purpose. There are various reasons why antidepressants may be prescribed for insomnia. For both the SSRIs and the TCAs, there is recognition that sleep disturbance is a core symptom of depression, and a hope that resolution of depressive symptoms may be associated with improvements in sleep. In addition, many physicians believe the SSRIs promote sleep. This perception is based on data generated from studies in patients with depression that showed perceived improvement in sleep based on patient-rated scales; unfortunately, this is more related to improvement in mood than actual improvement in sleep. SSRIs tend to lighten and fragment sleep, and it has become a common clinical practice to use a sleep-promoting agent, either a primary hypnotic or a sedating antidepressant, in combination with these drugs.

The most likely reason that TCAs and trazodone are prescribed to patients for insomnia is that their antihistaminic side effects promote sleep. These medications are inexpensive and are generally available as generics, so there are no formulary limitations. They are not controlled substances, so they do not require special prescriptions and have no refill limitations. There is some debate as to whether giving an antidepressant medication to patients with insomnia confers an antidepressant benefit in addition to a sleep-promoting benefit. This idea would make sense, but the doses of antidepressants that are given to patients for insomnia are typically very low. For example, trazodone is usually effective as an antidepressant at doses of 300 to 400 mg/day, but when trazodone is prescribed for insomnia, it is usually given at doses of 50 to 100 mg/day. However, dosing of TCAs and trazodone for sleep is by no means standardized, and the broad range of doses used for these agents in off-label use for treatment of insomnia is another differentiating point between the TCAs and trazodone and approved hypnotic medications.

Although physicians who are not sleep specialists may not realize it, the efficacy of TCAs and other antidepressants in treating insomnia is not well-demonstrated. Most of the data that do exist have been generated by looking at the sleep of patients with depressive disorders as their primary complaint. One study by Walsh et al.[4] in a population of patients with primary insomnia (N = 306) compared the hypnotic efficacy of trazodone and zolpidem. Patients were randomly assigned to receive 50 mg/day of trazodone, 10 mg/day of zolpidem, or placebo for 14 days. Effectiveness of the medication was assessed with a daily questionnaire and weekly office visits. In the first week of treatment, trazodone and zolpidem both reduced sleep latency significantly more than placebo ($p < .01$ and $p < .001$, respectively). In the second week of treatment, zolpidem reduced sleep latency significantly more than placebo did ($p < .005$), but trazodone did not (Figure 1). With regard to reported sleep duration, the effectiveness of zolpidem did not differ significantly from that of trazodone at the end of week 2. Although the results of this study are not conclusive, they suggest that the hypothesized long-term benefits of antidepressants in the treatment of insomnia are not as strong as they are thought to be.

Figure 1. Self-Reported Sleep Latency for Patients Given Trazodone, Zolpidem, or Placebo[a]



[a]Reprinted from Walsh et al.[4]
*$p < .01$ compared with placebo.
**$p < .001$ compared with placebo.

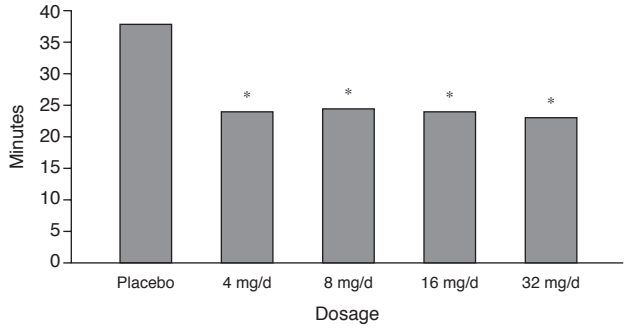
A major issue in the prescribing of antidepressants for the treatment of insomnia is their side effects. Antidepressant medications, including the SSRIs, the TCAs, and trazodone, now carry a warning about suicidality in patients with depression. The TCAs and trazodone have been found to cause serious side effects such as orthostasis, and thus increased risk of falls, and lethality in overdose, as well as more minor effects such as headache and nausea. Trazodone is also associated with cardiovascular side effects and residual sedation and carries a warning about priapism.

Antipsychotics and Anticonvulsants

Along with the antidepressants, atypical antipsychotics and anticonvulsants are also being prescribed off-label for insomnia. Many of the reasons for their popularity are the same as for the antidepressants. They are available within formularies and are not controlled substances. Prescriptions for these medications tend to be questioned less by formularies than prescriptions for benzodiazepine receptor agonists because they are generally given for serious psychiatric conditions, and most administrators would assume that if a physician has prescribed an antipsychotic or an anticonvulsant, then the patient must "really need it." Indeed, these medications may be of benefit for patients who suffer from both insomnia and an underlying psychiatric disorder.

Although these medications are generally readily approved by formularies, they tend to be quite expensive. The doses used in treatment of insomnia are uncertain,

Figure 2. Polysomnographically Measured Latency to Persistent Sleep in Patients Given Ramelteon[a]



[a]Data from Erman et al.[8]
*p < .001 compared with placebo.

Table 1. General Sleep Hygiene Techniques

Wake up at the same time of day
Obtain morning light exposure
Restrict napping or, if napping, be aware of the impact that napping has on nighttime sleep
Discontinue caffeine 4 to 6 hours before bedtime
Avoid alcohol and heavy meals close to bedtime
Exercise in the afternoon, but not within 3 to 5 hours of bedtime
Reduce arousal in the hours before bedtime
Minimize noise, light, and excessive temperature during the sleep period
Reduce interruptions that make it difficult to stay asleep
Read in bed only if it is relaxing, and then use a low light level and read appropriate materials
Avoid work, computers, and emotional stress in the bedroom
Use the bedroom only for sleeping and sexual activity
Move the alarm clock out of sight after it has been set for morning awakening

since there are no published studies demonstrating the effectiveness of these agents in patients with primary insomnia. The risk of side effects with these medications is high. With the antipsychotics, serious possible side effects include neuroleptic malignant syndrome, tardive dyskinesia, metabolic syndrome, hyperglycemia, diabetes mellitus, and weight gain, which is a common but difficult problem. Side effects with the anticonvulsants include hepatic failure and Stevens-Johnson syndrome, which are potentially fatal. Seizures, weight gain, and residual sedation are also of concern with the anticonvulsants.

Melatonin Agonist Compounds

Melatonin agonists have long generated interest with regard to treatment of insomnia because of the role of melatonin in the regulation of circadian rhythms. In the United States, melatonin is treated as a food additive even though it is a hormone. Little is known about its safety for general use.

Recent research into the use of melatonin to promote sleep has focused less on the direct administration of melatonin and more on the development of compounds that will have an effect on the brain's melatonin (MT) receptors. One of these compounds, ramelteon, a melatonin receptor agonist, has recently been approved by the FDA for treatment of insomnia at a dose of 8 mg/day. It has a high selectivity and potency at the MT_1 receptor site, which is thought to regulate sleep, and at the MT_2 receptor site, which is thought to regulate the circadian rhythm. This compound has been demonstrated to be more effective in promoting sleep than melatonin itself.[5,6]

Ramelteon is not a controlled substance. In a recent study[7] using standard methodology to assess abuse potential, "drug liking" and "street value" for ramelteon were not seen at doses of 16 mg/day, 80 mg/day, and 160 mg/day, doses that are 2, 10, and 20 times the 8 mg/day therapeutic dose, respectively. In an earlier study[8] of ramelteon in the treatment of patients with chronic primary insomnia, doses of 4 mg/day, 8 mg/day, 16 mg/day, or 32 mg/day of ramelteon or placebo were given to 107 patients for 2 consecutive nights. After a 5-day or 12-day washout period, patients were treated again with a different dosage; this was repeated until patients had completed a total of 5 treatment periods. The patients had a significantly ($p < .001$) shorter mean latency to persistent sleep when given any dosage of ramelteon than when they were given placebo (Figure 2). No increased benefit was found with higher doses. In a subsequent placebo-controlled study[9] of ramelteon (8 mg or 16 mg/day) in 405 adults with chronic insomnia evaluated with polysomnography, a statistically significant ($p < .001$) reduction in mean latency to persistent sleep was observed in the treatment group compared with placebo. In addition, total sleep time and sleep efficiency improved with no rebound insomnia or withdrawal effects.

NONPHARMACOLOGIC THERAPIES

Nonpharmacologic therapies should always be a component in the overall treatment of the insomniac patient. Various strategies, including sleep restriction, stimulus control, relaxation, and cognitive therapies, can benefit patients. However, there are limitations in the capacity of physicians to use these treatments, based on the practical limitations of reimbursement and availability of services as well as the motivation of patients.

Sleep Hygiene

Sleep hygiene is an essential part of treatment for insomnia and should be included in every treatment plan (Table 1). Although regularity of nighttime habits is good, when a patient is beginning therapy, establishing a regular morning wake time and trying to obtain morning light exposure are more important than going to bed at a regular time every night. It is better for patients with insomnia to go to sleep when they feel sleepy than to go to bed accord-

ing to the clock. Over time, as patients practice better sleep hygiene techniques, they should be better able to feel sleepy at a fairly regular time every night.

Patients should be educated about the impact of naps on sleep. If they nap, they should be aware that the sleep they obtain in the nap is going to diminish their capacity to fall asleep and stay asleep that night. However, if the sleep obtained in the nap will benefit the patient by keeping him or her more alert and active through the afternoon or evening, it may be acceptable, as long as the patient is aware one effect of the nap may be to reduce his or her sleep drive that night.

Patients should also be educated on how to prepare for sleep. Discontinuing caffeine several hours before bedtime and avoiding alcohol and heavy meals close to bedtime are part of good sleep hygiene for all insomnia patients. Exercise should be encouraged, but not within several hours of bedtime. Patients are often surprised to be told that they should avoid exercise before bed, as their perception is that exercise will tire them out and promote sleep. However, exercise is alerting, at least transiently, and it may have an impact on the regulatory elements of sleep such as core body temperature.

It is also important for patients to avoid activity that is mentally arousing before they try to sleep. Many patients may work at home in the evening, play video games, watch action movies, or participate in other activity that is very arousing up to the point at which they would like to go to sleep; they then may be surprised that they cannot immediately fall asleep. All these activities promote mental and emotional arousal and can interfere with the capacity to fall asleep.

Reading is an issue that often comes up when discussing sleep habits with patients. Although some physicians recommend that patients do not read in bed, for most patients I find that reading in bed, using a light source of low intensity, is acceptable for patients who report that reading helps them to relax and fall asleep. An important factor with regard to reading at bedtime is that the patients read appropriate materials. These include, for example, classic novels, spiritual or religious materials, biographies, and professional journals, but do not include popular mystery or action novels or magazines.

Patients should also be encouraged to use relaxation techniques to reduce arousal in the hours before bedtime. Techniques such as progressive muscular relaxation, focused imagery, or yoga exercises may be of benefit. For some patients, simple interventions such as listening to relaxing music or relaxation tapes or taking a warm bath may help to promote lower levels of arousal and facilitate sleep.

Attention to the bedroom environment is also important in improving patients' sleep habits. The bedroom should be as quiet, dark, and comfortable as possible. Patients often do not fully appreciate the impact of light, noise, and temperature regulation or the interference to sleep that may be generated by other family members or pets. Patients may have bed partners who get up and turn on lights in another room as they get dressed to go to work early in the morning or cats or dogs who wake them up too early. These interruptions, understandably, may disrupt the sleep of patients with insomnia and may provide an additional burden and source of distress to patients who have sleep initiation difficulties as well. The clinician should encourage these patients to address the sources of these interruptions to try to increase the probability that patients may be able to get a full night's sleep.

Another important part of good sleep hygiene is avoiding work or emotional stress in the bedroom. Many patients will use their laptop computers in the bedroom when they have trouble sleeping, either for work or to play games that they think will be relaxing and promote sleep. Unfortunately, this practice is likely to delay sleep onset, since it involves motor activity, light exposure, and cognitive stimulation, all of which interfere with sleep initiation. The bedroom should be used only for those activities that promote rest and sleep, which means that patients should avoid business and financial issues, household or family conflicts, or other sources of stress in their bedrooms. Moving the alarm clock out of sight after setting the alarm for morning awakening is a good strategy that most patients can use to promote sleep, since looking at the clock frequently during the night leads to greater arousal and disruption of sleep.

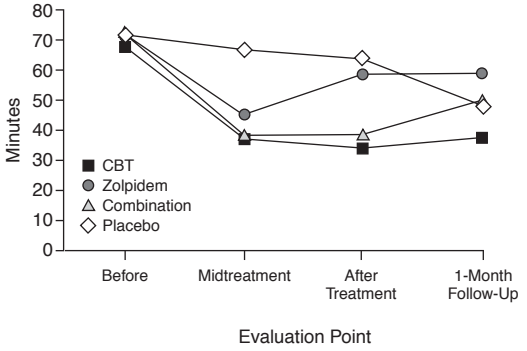
Cognitive-Behavioral Therapy

Cognitive-behavioral therapy (CBT) for sleep typically involves a multicomponent approach that includes elements of education about sleep hygiene, stimulus control, and cognitive psychotherapy. It can be performed either on a one-on-one basis or in a group approach.

The value of CBT for the treatment of insomnia has been evaluated in several studies.[10–12] A recent study by Jacobs et al.[12] compared CBT alone to pharmacotherapy alone and to a combination of CBT and pharmacotherapy. To be included in the study, patients had to be able to discontinue taking their medication for at least 4 weeks prior to entry into the study. Several patients who passed initial screening and wanted to take part in the study could not successfully discontinue their medication and were excluded. The patients who were able to discontinue their medication and participate in the study were thus likely to be highly motivated to succeed with the CBT. These patients (N = 63) were randomly assigned to 1 of 4 treatment arms: CBT alone, pharmacotherapy alone, CBT plus pharmacotherapy, and placebo.

The patients who were given CBT received 4 individual 30-minute treatment sessions and 1 telephone treatment session in a 6-week period.[12] The treatment sessions included sleep restriction, stimulus control, relaxation training, and education. The patients who were given

Figure 3. Sleep Onset Latency in Patients Given Cognitive-Behavioral Therapy (CBT), Zolpidem, CBT Plus Pharmacotherapy, or Placebo[a]



[a]Data from Jacobs et al.[12]

pharmacotherapy received 28 consecutive days of zolpidem at 10 mg/day, 7 consecutive days of zolpidem at 5 mg/day, and 5 days of alternate-day zolpidem at 5 mg/day. Patients completed diaries at 1, 3, 6, and 12 months after treatment and were assessed by the research team 8 weeks after treatment.

At the conclusion of treatment, the patients who received CBT alone and CBT plus pharmacotherapy showed significantly ($p \leq .03$) greater improvement in sleep latency than the patients given pharmacotherapy alone or placebo (Figure 3). The patients who received CBT alone showed a better outcome than the other 3 groups at the 1-month follow-up. Patients who received CBT alone or were treated solely with medication had sustained benefit at 12 months with regard to sleep onset latency.

In this study,[12] CBT showed clear advantages over pharmacotherapy alone for the treatment of insomnia. CBT improves patients' understanding of the disorder and improves compliance with medications. CBT does have some limitations, however. Access to providers of CBT can be limited and expensive, and CBT requires a longer period of time to generate initial therapeutic effects than medication treatment. Patients must be motivated to learn and practice CBT and must have enough patience to wait for the expected therapeutic effects of this treatment.

EMERGING THERAPIES

New medications are being developed that have modes of action similar to those already available on the market. Indiplon, discussed earlier, is a new nonbenzodiazepine benzodiazepine receptor agonist in development. Another medication in development, gaboxadol, works through the GABA system, as do the benzodiazepine receptor agonists, but appears to interact with an extrasynaptic GABA receptor recognition site and mediates its effects via a GABA-A receptor population that is different from that modulated by benzodiazepine receptor agonists. As detailed above, modified-release formulations of currently available and new medications are being developed to lengthen the duration of action of hypnotic compounds, with the expectation that this will prolong the therapeutic effects of these agents and extend total sleep time for patients.

Medications that have different mechanisms of action from those that are currently on the market are also being studied. Use of serotonin-2A receptor agonists in treatment of insomnia is being studied, as are medications that are designed to work via corticotropin-releasing factor mechanisms. It is possible that these agents, if developed, and other new types of medications using novel mechanisms may have a lower abuse potential and less chance of residual sedation than medications currently available for the treatment of insomnia.

Drug names: chlordiazepoxide (Librium and others), diazepam (Valium and others), estazolam (Prosom and others), eszopiclone (Lunesta), flurazepam (Dalmane and others), morphine (Avinza, Oramorph, and others), quazepam (Doral), ramelteon (Rozerem), temazepam (Restoril and others), trazodone (Desyrel and others), triazolam (Halcion and others), zaleplon (Sonata), zolpidem (Ambien).

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

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