TREATMENT OF INSOMNIA*

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ABSTRACT
Any treatment for insomnia should accomplish 3 goals: induce sleep, maintain sleep, and promote functionality the next day. Insomnia treatments include behavioral, cognitive, or pharmacotherapy, alone or in combination. In general, behavioral and/or cognitive therapy should be part of any first-line approach. Before any treatment is administered, it is necessary to determine the type of insomnia (eg, trouble falling asleep or trouble staying asleep) in addition to ensuring commitment from the patient to make sleep a priority and offer commitment from the healthcare practitioner to be available for the long term. This article reviews the available behavioral and cognitive therapies for which there is evidence of their benefit (ie, relaxation training, stimulus control therapy, sleep restriction, sleep hygiene education, and cognitive therapy). Many behavioral therapies can be conducted by a primary care practitioner. The article also reviews the 3 treatment strategies for pharmacotherapy (ie, antihistamines, γ-aminobutyric acid receptor agonists, and melatonin receptor agonists). A brief discussion of newer drug therapies also is included. The goal of any treatment for insomnia is, essentially, to go to sleep, stay asleep, and feel good the next day. To determine the best treatment for a particular patient, it is necessary to determine the type of insomnia (eg, trouble falling asleep or trouble staying asleep), which is best measured by using a sleep diary for 2 weeks.

Insomnia treatments include behavioral, cognitive, or pharmacotherapy, alone or in combination. In general, behavioral and/or cognitive therapy should be part of any first-line approach, because not every patient wants or is willing to take medication for insomnia, and pharmacotherapy may be contraindicated for some patients. Also, as will be discussed, although pharmacotherapy is especially useful for treating acute insomnia, behavioral and cognitive therapies not only increase the chances of treatment success but also are more effective at preventing future insomnia episodes.

BEHAVIORAL THERAPY
Behavioral therapy is designed to tighten the relationship between sleep behavior and bedtime. It is accomplished through establishing rituals that promote better sleep. The disadvantage with behavioral therapy is that it can take up to 12 weeks or longer to affect sleep quality.

For a patient to extract the most benefit, behavioral therapy requires a commitment by the patient to make sleep a priority, specifically to take stock of his or her personal sleep needs, face up to his or her sleep problems, learn to manage sleep crises, take age into account (because sleep needs differ throughout life), and adopt a sleep-smart lifestyle. The best and most effective way to improve sleep hygiene is to adopt a regular schedule, in particular maintaining a regular sleep schedule 7 days per week. This can even be written as a "prescription" for the patient. Other more regimented therapies include sleep restriction, stimulus control, and relaxation training.
Sleep restriction ensures that time in bed is equal to time asleep. This will avoid the anxiety of lying awake in bed, worrying about sleep, and increasing the association of sleep as an unpleasant or stressful experience. Sleep restriction usually starts by asking the patient to identify how many hours of sleep he or she is getting. Maintaining a sleep diary may be necessary to accurately determine this. If the patient says, “I’m only sleeping 5 hours a night,” restrict bedtime to only 5 hours (eg, going to bed at midnight and waking at 5:00 AM). This initially creates a sleep debt and the patient will be very tired the first few days, but often it also relieves anxiety about going to sleep. Also, because patients with insomnia mistakenly spend extra time in bed trying to fall asleep, sleep restriction ensures that the sleep debt accumulates to such a degree that sleep will more easily follow. The allotment of restricted sleep time (which should not be less than 5 hours) can then be added to by 15 to 30 minutes per week, until it builds up to a sleep duration that is best for the patient. Although it produces the most rapid changes in sleep patterns, some patients may not be motivated to pursue this type of therapy.

With stimulus control, the patient must examine not only the environment in which he or she sleeps, but also the environment that he or she is letting go of when succumbing to sleep. Depending on the patient, this may involve removing reminders of insomnia (eg, a clock), removing any physical stimuli that can prevent sleep onset or duration (eg, a snoring spouse, a pet, or a television), using the bed only for sleeping and sexual relations (ie, no paying bills, working, eating, or watching television in bed), and sleeping only in bed (with no napping). Stimulus control also tightens the relationship between going to bed and going to sleep by requiring the patient to get up and out of bed if he or she is unable to fall asleep in 15 to 20 minutes and doing something until the patient is tired again. This can be repeated as often as necessary. Finally, the patient should avoid any activity that may stimulate the mind before bedtime, such as checking e-mail, watching the news, or discussing a topic that causes anger or angst.

In the place of these stimuli are relaxation techniques that help to quiet the mind, relax the body, and create bedtime rituals, which also help to foster sleep hygiene. These techniques can include reading, listening to music, praying or meditating, a hot bath, comfortable pajamas (or sleeping nude, if that is a patient preference) and linens, cooler bedroom temperature, and being only slightly hungry. Because these techniques can sometimes induce performance anxiety, the selected technique should be started during the day, when there is no pressure or expectation of sleep, and practiced regularly.

The other possible advantage with relaxation techniques is that they can be self-taught, which can lower healthcare costs. A recent small study by Morin et al illustrated the benefit with this type of program. A total of 192 patients with insomnia were randomized to no treatment or a self-help program, which consisted of 6 educational booklets mailed weekly. The booklets provided information on insomnia, healthy sleep practices, behavioral sleep scheduling, and cognitive strategies. After 6 months of follow-up, the intervention effectively improved all measured insomnia symptoms. The improvements were statistically significant, but clinically modest. The authors note that the study had several limitations, including poor compliance (43%–62%) and a changing patient population (ie, approximately 50% of patients had a different sleep status between study selection and randomization). The authors note that “it is plausible then that additional social support, feedback, and reinforcement throughout intervention, perhaps through telephone consultations, could improve both compliance and outcomes.”

Nurse practitioners (NP) are ideally suited for this but, ironically, are not reimbursed by insurance companies for this type of care.

**Cognitive Therapy**

Sleep behavior is learned. Our attitudes and beliefs about sleep were instilled in us from our parents. Therefore, the first step in cognitive therapy for insomnia is to determine how the patient perceives sleep (eg, Is sleep a priority? How much sleep do you think you need?). Many patients misjudge how much sleep is optimal for them, perhaps thinking they only need 6 hours of sleep when they need more or focusing on getting 8 hours of sleep when they may not need that much. Other common misconceptions about sleep include myths (eg, the best sleep is before midnight) or fear of “going crazy” or becoming psychotic or dying without sleep. In fact, it has never clearly been shown that lack of sleep causes psychosis. Cognitive therapy involves restructuring (ie, challenging and replacing) anxiety-producing and erroneous beliefs about sleep and sleep loss. Cognitive therapy is usually administered by a mental health professional or a clinician who specializes in sleep disorders.

Cognitive therapy is an important treatment option because it offers both short- and long-term benefits,
particularly when combined with behavioral therapy (Figure 1). Therefore, it also can prevent future episodes of insomnia or better prepare the patient in handling these episodes when they do occur. Cognitive therapy also can help distinguish cases of true insomnia from age-related sleep changes and to reduce the emotional distress that insomnia ultimately inflicts.

**Cognitive-Behavioral Treatment**

Cognitive and behavioral treatments can be administered separately, but most clinical research has focused on their combination: cognitive-behavioral therapy (CBT). CBT is especially useful in addressing perpetuating factors that contribute to insomnia. In chronic insomnia, the patient inadvertently creates a vicious cycle of impaired sleep, fatigue, worry about sleep, excessive time in bed or napping to make up for the sleep debt, and ultimately creating physical and emotional arousal, which further inhibits sleep. Pharmacotherapy is often best used to break this cycle of sleep debt, whereas CBT is used long-term to prevent recurrence, as evidenced by several studies. Although most of the discussion here has focused on primary insomnia, CBT also benefits patients with secondary insomnia. However, little is known about its usefulness for insomnia caused by jet lag, acute stress, or shift work.

**The Nurse Practitioner’s Role in CBT**

A key component in CBT is for NPs to monitor patterns of the patient and the bed partner. CBT requires making sleep a high priority for all sleepers in the household. Educating the patient about sleep architecture and what it means for better sleep outcomes is very important. Also, seeing the patient on a weekly basis while therapy is being employed allows for feedback and support and the chance for the patient to develop insight and judgment about barriers to getting to sleep and staying asleep.

**Pharmacotherapy**

By the time many patients with insomnia present to a healthcare practitioner (HCP), they usually are desperate for a “quick fix,” saying, “Just knock me out. I’m so tired of being tired.” For patients unwilling to pursue behavioral and/or cognitive therapy, or in whom the insomnia is not resolved, there are several medication choices. However, the specific medication must produce sleep that is of the same quality and consistency as a normal night’s sleep—that is, the patient should be able to fall asleep easily, stay asleep, and be functional the next day.

There are many neurotransmitters involved in the sleep-wake cycle: sleep promoting (ie, adenosine, melatonin, galanin, and γ-aminobutyric acid [GABA]) and wakefulness-promoting (ie, norepinephrine, orexin, etc.).

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**Figure 1. Long-term Outcomes with CBT vs Medication for Insomnia**

In this study, 78 adults with chronic primary insomnia were randomized to receive CBT (ie, stimulus control, sleep restriction, sleep hygiene, and cognitive therapy), pharmacotherapy, both (Comb), or placebo. Outpatient treatment lasted 8 weeks and follow-ups continued at 3, 12, and 24 months. Efficacy is defined as a decrease in the number of minutes awake after sleep onset, which is the sum of the duration of all awakenings between sleep onset and final wake-up time.

CBT = cognitive-behavioral therapy; Comb = CBT and pharmacotherapy; FU = follow-up.

Adapted with permission from Morin et al. *JAMA*. 1999;281:991-999.

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**Figure 2. Drugs Used to Treat Insomnia**

*Not approved by the US Food and Drug Administration for this use. BZD = benzodiazepine; BZRA = benzodiazepine-receptor agonist.

Adapted with permission from Walsh. *Sleep*. 2004;27:1441-1442.
acetylcholine, dopamine, and histamine). Medications prescribed for insomnia work primarily by affecting 1 of 3 neurotransmitters: histamine, GABA, and melatonin. Although many drugs frequently are prescribed in the attempt to treat insomnia (Figure 2), most do not have a US Food and Drug Administration (FDA) indication for this use.

**Histamine**

Histamine is an excitatory neurotransmitter, therefore, antihistamines cause sleepiness. Antihistamines are the second most commonly used drug in the United States to treat insomnia (after alcohol). Antihistamines can be obtained over-the-counter (OTC) or by prescription, but they do not have US FDA approval for treating insomnia. Diphenhydramine is probably the most well-known antihistamine, but many patients also take Tylenol PM, which is 25-mg diphenhydramine and 500-mg acetaminophen. These antihistamines are relatively inexpensive and, because they have no abuse potential, they are not scheduled by the US Drug Enforcement Administration (DEA). However, many patients mistakenly think that because these drugs are OTC, they can safely take virtually limitless quantities for insomnia. However, these medications have an 8- to 15-hour half-life, which leads to daytime sedation and potential danger of overdose. Patients also can develop a tolerance to them over time.

Several antidepressants also have histamine as a secondary binding characteristic; these include trazodone (used frequently to treat insomnia), paroxetine, mirtazapine, fluvoxamine, and, in general, tricyclic antidepressants (eg, clomipramine, amitriptyline, and nortriptyline)

However, these drugs also lack US FDA approval for treating insomnia and also have potential for side effects, which should be weighed when creating a long-term treatment strategy for insomnia. This is especially important in elderly patients.

**γ-Aminobutyric Acid**

Drugs that activate GABAergic neurotransmission have been studied extensively, and several drugs with this mechanism of action have indications for the treatment of insomnia. Virtually all of these drugs enhance GABA, receptor activity and are referred to as sedative-hypnotics. Sedatives decrease activity, moderate excitement, and calm the recipient; hypnotics produce drowsiness and facilitate the onset and maintenance of natural-type sleep (ie, the person can be easily awakened and electroencephalography recordings are similar to those with naturally occurring sleep).

Barbiturates were the first drugs found to affect GABAergic neurotransmission; however, the most frequently prescribed and well known are the benzodiazepines. Most benzodiazepines are quickly absorbed. The primary differences between them lie in their relative elimination half-lives, which can range from less than 4 hours to more than 1 week (Figure 3). The variety of half-lives with these drugs makes them especially useful for managing different types of insomnia, but also highlights the importance of carefully documenting insomnia symptoms, such as difficulty falling asleep versus difficulty staying asleep. Patients having trouble falling sleep should use drugs with short half-lives, whereas patients waking up after only a few hours would fare better with intermediate to longer half-life drugs. Patients often report increased total sleep time as the litmus test for a good night's sleep (eg, "I slept 8 hours last night" or "I didn't wake up once last night"). The

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life, hrs</th>
</tr>
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<tbody>
<tr>
<td>Zaleplon</td>
<td>1</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>2</td>
</tr>
<tr>
<td>Triazolam*</td>
<td>3</td>
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<td>Quazepam*</td>
<td>39</td>
</tr>
<tr>
<td>Flurazepam*</td>
<td>74</td>
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* Benzodiazepines
Several commonly used benzodiazepine and nonbenzodiazepine γ-aminobutyric acid agonists and their half-lives are shown. Half-lives can extend to beyond 1 week for some drugs, such as medazepam, nordazepam, and prazepam. Data from Dikeos and Soldatos.
longer the medication’s half-life, the greater the opportunity for increasing total sleep time, and there is less chance of wake after sleep onset. However, correct timing of the dose is important and requires close patient monitoring to minimize the risk of driving (or working) drowsy in the morning.

In fact, there are several limitations with using benzodiazepine and nonbenzodiazepine GABA receptor agonists. For example, all of these medications are classified as schedule IV controlled substances by the US DEA. Also, some of the side effects associated with their use include psychomotor impairment, depressed respiration, and amnesia. Patients taking these drugs over a long period of time also can suffer from rebound insomnia when the medication is stopped and/or tolerance to the drugs over time. Also, overdose is a potential danger with these drugs.

Nonbenzodiazepines are the most recently available drugs in this class. They include eszopiclone (indicated for sleep onset and maintenance, and the first hypnotic to be approved without a short-term use limitation), zaleplon (indicated for sleep onset, but sufficiently short-acting to be taken late during the night), and zolpidem (indicated for improving sleep onset and total sleep time). Controlled-release zolpidem is approved for treating insomnia associated with difficulty initiating and maintaining sleep.

**Complementary Medicine**

Although an HCP need not endorse or reject complementary medicines for the treatment of insomnia, it is important to be aware of what patients are consuming or even reading about these products. For example, valerian root and kava kava are commonly touted as insomnia treatments. The biggest potential hazard with these treatments is lack of standardization in their production (noted in a July 2001 *New York Times* article by Nagourney). Both HCPs and consumers can check to see if a particular product has been tested for content (www.consumerlab.com).

**Melatonin Agonist**

Recall that melatonin is one of the critical regulators of the circadian rhythm. Its secretion is controlled by the suprachiasmatic nuclei (SCN), increasing as drowsiness sets in, with maximal levels at approximately 3:00 AM to 4:00 AM. Melatonin has been used to shift the sleep-wake cycle in people suffering from jet lag or shift work insomnia. It is available as a dietary supplement. Ramelteon is a potent and selective melatonin receptor agonist and received US FDA approval in July 2005 for sleep onset insomnia. Importantly, it is not a scheduled drug by the US DEA, it carries no risk of abuse or tolerance, and it does not impact GABA or histaminic neurotransmission. It is the first drug in 35 years to act outside of those 2 neurotransmitter systems.

Ramelteon acts on melatonin 1 (MT1) and melatonin 2 (MT2) receptors, which are heavily concentrated in the SCN. Given the key role of the SCN in sleep regulation, agents with high affinity and selectivity for MT1 and MT2 receptors are rational targets in the treatment of insomnia. Specifically, binding to MT1 receptors could decrease SCN stimulatory output (the alerting signal). These effects are in addition to the melatonin already available and active in the body. With the alerting mechanism inhibited, the “sleep switch” is able to turn on. Agonism of the MT2 receptors may help to entrain the circadian clock through phase shifting, which could help adjust the timing of sleep. To date, the most common side effects observed are sleepiness, dizziness, and fatigue. As with any other medication for the treatment of insomnia, patients should avoid driving or operating machinery for a few days until they know how the drug will affect them the next day.

**Drugs Under Investigation**

Also under investigation are several other new drugs. Gaboxadol is GABA receptor agonist, but it acts only on certain types of GABA receptors (ie, outside synaptic junctions of thalamic and cortical neurons), which are thought to play an important regulatory role in the onset, maintenance, and depth of the sleep process. Also in phase III clinical trials are low-dose doxepin (a tricyclic antidepressant) and indiplon (a short-acting benzodiazepine receptor agonist hypnotic).

**The Nurse Practitioner’s Role in Prescribing**

The NP’s role in prescribing any of these medications is to match the insomnia symptom with the most appropriate treatment option. However, each state has its own prescriptive authority guidelines for NPs regarding scheduled medications. Once the medication is started, consistent follow-up is important to ensure that the dosage meets the specific needs of the patient and that behavioral interventions also are employed.
CONCLUSIONS

Behavioral therapy focuses on sleep restriction, stimulus control, relaxation, and sleep hygiene education, whereas cognitive therapy restructures anxiety-producing or erroneous beliefs about sleep. Medications treat 3 targets in sleep regulation: GABA, histamine, and melatonin. A multifaceted approach to treating insomnia appears to be most effective—one that can provide immediate relief, allay patient fears and anxiety that may have developed over sleeping, and maintain these benefits over the long term. Studies have shown that CBT is beneficial for “primary” and “secondary” insomnia, maintains benefits long term, and when used with pharmacotherapy can improve patient outcomes even further. The NP’s role is to monitor and educate the patient and the bed partner, to ensure that sleep is a high priority in the household, and to maintain close follow-up. If medication is required, the NP will ensure that the medication matches the insomnia symptoms. Given the strength of data regarding insomnia treatments, future research questions include the timing of CBT versus pharmacotherapy (eg, concurrently or sequentially), optimal treatment dosage (ie, timing and frequency of follow-up consultations), and whether maintenance treatment will enhance long-term outcomes.2,36

REFERENCES