



# Sleep

## A Primer for



**Controlling this very common condition often means focusing as much on the mind as the body.**

# Aids:

## Insomnia Treatment

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**T**he British scholar and novelist C.S. Lewis once said, “Many things—such as loving, going to sleep, or behaving unaffectedly—are done worst when we try to do them.” While we all have our own experiences about loving and behaving unaffectedly that testify to the veracity of this statement, anyone who suffers from insomnia can verify the part about sleeping to be true.

Every night millions of Americans lay awake in bed as they wrestle with perhaps the most common disorder afflicting otherwise healthy adults: delayed and/or restless sleep. Most of these people have come to accept this as a fact of life and see their beds as a nightly battleground where they struggle in the darkness to achieve a few hours of peace. Sadly, many of them do not know that it doesn't have to be that way, and they never talk to their primary care physician about their difficulty achieving restful sleep. And of those who are aware they could have a problem, many often try to self-medicate with over-the-counter treatments, home remedies or alcohol.

But with the increasing public awareness of the prevalence of sleep disorders such as insomnia, more people may be ready to start talking to their physicians about what's keeping them up at night. This means there is also a need for more awareness among the medical community of how insomnia treatments work. Although biological aspects play an important role in the condition, for many the bedrock of therapy is psychological and behavioral—that is, helping patients learn how to control their minds enough to keep them still and see their beds as a restful place. This is not to say that there are no medical treatments available, of course. In fact, several promising new medications for insomnia can, in the right settings, be very helpful.

In this article, we'll review how to treat insomnia by looking at both the psychiatric and pharmacological techniques that can help patients get to sleep.

# Insomnia Treatment

## The Reasons for Restlessness

When evaluating a patient for insomnia, it's important to focus on the core of the disturbance and make the recommendations around this. Insomnia is often a symptom of another disturbance, such as depression, and if this is the root problem then it should be treated. The same is true if the insomnia derives from a physical pathology, such as poorly controlled pain, respiratory disturbance or metabolic problem, to name just a few. Of course, sleep disorders are commonly secondary to neurological conditions as well. Managing the primary condition will help ameliorate the sleep disturbance.

For many chronic insomnia sufferers, especially those with primary insomnia, the best approach may be to use cognitive-behavioral treatment as the foundation for therapy. Pharmacological treatments will help initially, and we will discuss these later in the article, but a short-term course of such medications alone is unlikely to offer a viable long-term solution. And at this point in medicine, there is no clear algorithm of how to proceed with respect to the combination between cognitive-behavioral techniques and pharmaceutical intervention.

Hyperarousal in both the cognitive and metabolic sense is now identified as a common element underlying chronic insomnia. Patients often have cognitive distortions about sleep to the extent that they focus excessively, perhaps even obsessively, on going to sleep. Often they organize their lives around their ability to sleep and, in the process, develop maladaptive problems that adversely affect their lives in other ways.

The key here is to identify the problems, the thoughts and behaviors behind the insomnia. Patients should learn to recognize the stimuli that keep them awake and how to either avoid or control them. By learning the appropriate techniques, patients can stop "trying" to put themselves to sleep and actually close their eyes peacefully.

An example of one such a technique, stimulus control therapy, is to have patients get out of bed if sleep doesn't come within 20 minutes. Those who lay in bed awake and ruminate on not being able to sleep often become anxious and restless, and over time they begin to associate their beds with stressful situations. They can break these associations by restricting their time in bed to sleeping, and by keeping a sleep log to record when they go to bed and when they actually get to sleep. If they achieve 90 percent sleep efficiency, they can be considered to have their condition under control.

Other psychological and behavioral techniques ranging from muscle relaxation to hypnosis may also be useful. However, these should be used as an adjunct to such mainstays as stimulus control and corrective measures to the cognitive state. At present, the data and collective clinical experience suggests that these are not effective in their own right.

## Pharmacological Intervention

Insomnia's impact is pervasive, cutting across racial, gender and socioeconomic differences, and has a history stretching back thousands of years. Unfortunately, sleep in general and sleep disorders in particular are among the least understood physiological mechanisms common to mankind. So it may come as no surprise that modern pharmaceutical research has not yielded many successful medical interventions. Between the mid-19th century and the 20th century we went from using bromides to barbiturates, and it wasn't until the 1960s that the benzodiazepine class of drugs gave us relatively safe and effective options for treatment. These sedative-hypnotic medications, which include flurazepam, quazepam and estazolam, are still sometimes used, but concerns of abuse, dependence and adverse effects have led to a decline in how often they are prescribed.

In the 1990s the non-benzodiazepine, benzodiazepine receptor agonist class gave physicians finally gave physicians a few viable choices with better safety profiles. These include zolpidem (Ambien) and zaleplon (Sonata), both of which reduce the time it takes to get to sleep. They differ in that zolpidem's effects last longer and can help the patient stay asleep longer, so it must be taken at bedtime. In contrast, zaleplon may be taken at bedtime or later for patients who have difficulty falling asleep or after a nighttime awakening as long as there are several more hours left to sleep.

Just recently, insomnia treatments have become a rather hot area for pharmaceutical companies. Since 2004 there have been three new treatments brought to market, eszopiclone (Lunesta), ramelteon (Rozerem) and zolpidem tartrate extended-release tablets (Ambien CR). Another potential entrant into the market, indiplon from Neurocrine Biosciences, was recently rejected (the FDA ruled the 5mg and 10mg doses were approved but not the 15mg XR dose); the company said it plans to resubmit and hopes to have the drug available by January 2008.

Lunesta was approved in the form of 1mg, 2mg or 3mg tablets in December 2004 for treating insomnia. Like zolpidem and zaleplon, it acts as a GABA receptor agonistic modulator. Research shows it to be safe and effective for up to six months, with a 12 month open-label extension showing similar results. The most common adverse effects are dizziness and loss of coordination, and it may impact driving skills the next day.

In July 2005 the FDA approved Rozerem 8mg tablets for insomnia characterized by difficulty with sleep onset. It selectively targets melatonin receptors located in the suprachiasmatic nucleus (SCN) to alter the body's natural circadian rhythms. This treatment shows no risk of dependency and a negligible risk for next-day "hangover" effect, although it is associated with decreased testosterone levels and increased prolactin levels and should not be used by patients with severe hepatic impairment or in combination with fluvoxamine.

Ambien CR was given an FDA indication for insomnia in September 2005. The tablets, 12.5mg for adults and 6.25mg for elderly patients, contain two layers: the first dissolves quickly to aid sleep onset and the second helps sleep maintenance. There is a low occurrence of adverse effects that most frequently include drowsiness, dizziness and diarrhea.

The emerging data for the effectiveness of each treatment may help to link specific benefits with specific patients. For example, the longer-acting agents such as Ambien CR or Lunesta are most suitable for patients that have trouble staying asleep. In contrast, shorter-acting treatments such as Rozerem or Sonata would be more appropriate for sleep-onset insomnia. There are currently trials underway to better evaluate the nuances of these medications.

Over-the-counter sleep medications, the majority of which contain some form of anti-histamine such as diphenhydramine, are widely used. However, their effectiveness in the treatment of chronic insomnia has not been established and hence these medications are usually not recommended for this indication by sleep specialists. The same can be said for herbal preparations. In limited studies, valerian has shown some effectiveness in short-term trials. Virtually no controlled data exist for other herbals, some of which (e.g., kava) are potentially hazardous. Melatonin, available as a “nutritional supplement,” has been widely utilized to treat chronic insomnia. Although melatonin has some clear circadian phase-shifting effects, and is sedating in larger dosages, a clear scientific rationale for its use as an effective pharmacotherapy has not emerged.

These latest additions to the treatment regimen are certainly useful, but the prescription pad alone is not the place to find effective long-term solutions. At present optimal pharmacotherapy approaches for insomnia are not well defined; however, when medication is used, it should usually be combined with cognitive/behavioral therapy, ideally delivered by a therapist with some background and training in the psychological and behavioral treatment of these problems. The clearest indications for drug treatment remain acute or short-term insomnia.

The fact is that many if not most patients who are diagnosed with chronic insomnia have already failed at least one trial of a treatment, and often several, before they are referred to a sleep specialist. The best approach at that point is to focus on careful evaluation and the cognitive-behavioral approach.

### The Kennedy Connection

Ambien received a great deal of unwelcome attention in the mainstream media recently when Rep. Patrick Kennedy (D-R.I.) was involved in a vehicle accident near the Capitol. He claimed to have taken both Ambien for his insomnia and an anti-nausea drug that causes drowsiness. While other agents may have been at work in this situation, there has been a major focus on Ambien and its unpleasant effects in the mainstream media and it has

## The Criteria for Insomnia

The formal criteria for the identification of insomnia defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* are as follows:

- The predominant complaint is difficulty initiating or maintaining sleep, or nonrestorative sleep, for at least one month.

- The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

- The sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, or a parasomnia.

- The sleep disturbance does not occur exclusively during the course of another mental disorder (e.g., major depressive disorder, generalized anxiety disorder, a delirium).

- 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.

*The International Classification of Sleep Disorders (ICSD): Diagnostic and Coding Manual, American Academy of Sleep Medicine, 2nd edition* put forth the following general criteria for insomnia:

A. A complaint of difficulty initiating sleep, difficulty maintaining sleep, waking up too early, or sleep that is chronically nonrestorative or poor in quality. In children the sleep difficulty is often reported by the caretaker and may consist of observed bedtime resistance or inability to sleep independently.

B. The above sleep difficulty occurs despite adequate opportunity and circumstances for sleep.

C. At least one of the following forms of daytime impairment related to the nighttime sleep difficulty is reported by the patient:

1. Fatigue/malaise.
2. Attention, concentration, or memory impairment.
3. Social/vocational dysfunction or poor school performance.
4. Mood disturbance/irritability.
5. Daytime sleepiness.
6. Motivation/energy/initiative reduction.
7. Proneness for errors/accidents at work or while driving.
8. Tension, headaches, and/or GI symptoms in response to sleep loss.
9. Concerns or worries about sleep.

More specific criteria exist for each specific insomnia diagnosis.

## The Skill of Sleeping

The most traditional way of getting to sleep is to engage in a monotonous task such as counting sheep. It may be corny, but it can also be effective. Here are some other tips that patients can sue to control their sleep courtesy of the FDA:

- Avoid caffeine and caffeine-containing drugs, nicotine, and alcohol for four to six hours before bedtime.
- Do not exercise within four to six hours before bedtime.

- Perform a relaxing ritual before bed, such as taking a warm bath, listening to relaxing music, or having a light snack.

- Before going to bed, put your worries out of your mind. Plan to address them at another time.

- Reserve your bed for sleeping. Don't watch television or do work in bed.

- Go to bed only when sleepy. If you can't get to sleep within 15 to 20 min-

utes, get out of bed and do something relaxing for a while.

- Keep the bed comfortable and the bedroom conducive to sleep by making it silent and keeping the temperature comfortable.

- Wake up at around the same time every day, even on weekends.

- Don't take naps, or nap during the mid-afternoon for no more than half an hour.

even become the subject of a class-action lawsuit.

What's more, the studies of Ambien have shown that partial arousals are possible. In these situations, the patients find themselves caught between sleep and awakening. This can often happen when the individuals taking the medication fail to get into bed in a timely manner, and the result manifests in sleepwalking or night terrors. What's more, it is not clear that this effect is specific to Ambien and further research will be needed to see how prevalent it is among the other sleep treatments.

From a practical standpoint, the best way to handle such adverse effects is to counsel patients not to take medications until they're ready to get into bed in a timely manner. They should be warned about what sedating medications can do and what they should not do after taking one, such as consume alcohol. If the patient is concerned, he or she should speak to the physician immediately.

The same caveat applies to Rozerem, which should be taken within 30 minutes of going to bed when all following activities are related to preparation for bedtime. It should not be used by patients with severe hepatic impairment, or in combination with fluvoxamine. It is also associated with decreased testosterone levels and increased prolactin levels. Lunesta should also only be taken before bedtime, when the patient has at last eight hours to devote to sleep.

At follow-up, the physician should note any nocturnal occurrences associated with the medication. Safety always comes first in medicine, and if the adverse effects are unacceptable then it's time to consider a new direction.

## Better Nights Ahead

Insomnia may be largely undiagnosed at present, but it is quickly becoming recognized as less of an expendable luxury and more as a significant part of overall health. Some recent studies have demonstrated that restlessness can have a big effect on daytime life.

It may be impossible to put a price on a good night's sleep, but on April 5th the Institute of Medicine released a report entitled

"Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem" that quantified the cost of sleepiness. The total direct and indirect economic costs were said to be in the hundreds of billions of dollars per year "at a minimum," including lost business productivity (\$150 billion), motor vehicle accidents involving tired drivers (\$48 billion) and medical care for sleep disorders (almost \$16 billion). The report also noted that the effects of sleep loss and sleep disorders are associated with raised risks for hypertension, diabetes, obesity, depression, heart attack, and stroke, in addition to problems at work and in family life. However, many people fail to seek treatment for their condition because they fear the stigma of being labeled with a psychiatric disorder or they believe that health care providers cannot do anything to help them.

A new study presented on May 24th at the American Thoracic Society International Conference in San Diego indicated that sleep deprivation is also linked to weight gain. Researchers at Case Western Reserve University studied 68,183 women aged 40 to 65 years and reported both how many hours they got in a typical night's sleep and what their weight was at two-year intervals over sixteen years. The results showed that the women who slept less tended to gain more weight over time. After adjusting for age, those who slept for five or fewer hours per night gained 1.5 kg more during the next ten years than those who slept at least seven hours a night. Interestingly, the women who slept less also tended to eat less as well. The study's presenter, Sanjay Patel, MD, said the weight gain associated with sleep deficiency could be caused by either a lack of energy for exercise or possibly a change in a person's base metabolic rate.

As more of such studies raise awareness of the disorders that can stem from insomnia and other conditions, it's likely the public will start coming to terms with the importance of a good night's rest. Ideally, more people will realize that the way to win the war against sleeplessness is to follow a therapeutic strategy that combines careful assessment with a multifactorial approach to treatment. **PN**