

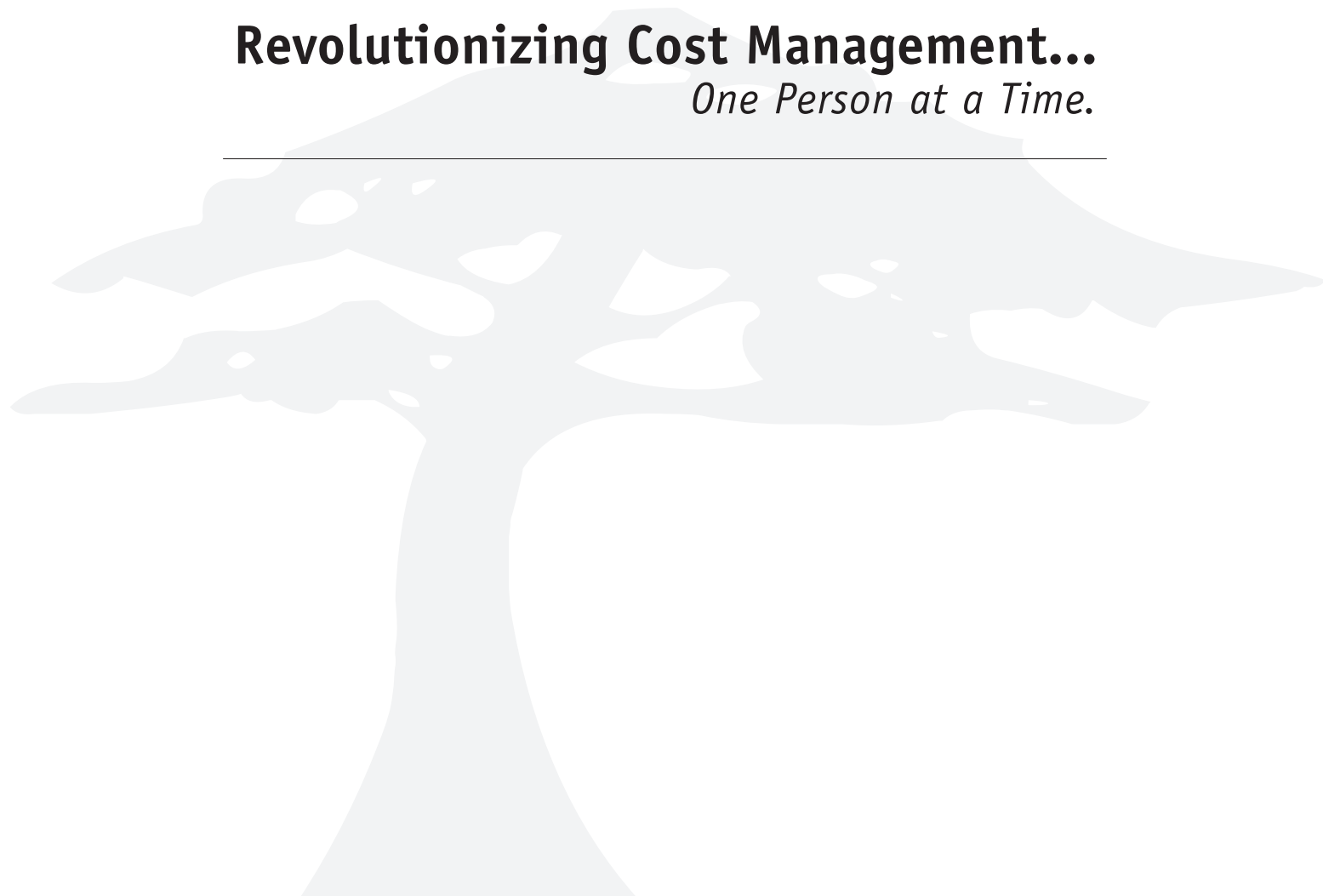


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# CHRONIC INSOMNIA AND ITS PHARMACEUTICAL TREATMENTS

JIM ANDREWS AND DEBRA CERRATO

## INTRODUCTION

Chronic insomnia, as related to injury or illness, can have a multitude of underlying causes. Following an on-the-job injury or a car accident, patients may worry about missing work, unfulfilled family obligations, and financial strain, all of which can cause sleepless nights, sometimes leading to the need for prescription insomnia medications. In other cases, an injury can require patients to become sedentary as they heal, and this decrease in normal energy expenditure may cause restlessness and insomnia. Or, for patients taking prescribed pain medications following an injury, building tolerance to the medication can also cause insomnia.

Approximately 25 percent of the long-term claims processed through Cypress Care include prescribed insomnia medication.

**OVERVIEW**

Insomnia is defined as difficulty with initiation, maintenance, duration, or quality of sleep — despite normal sleeping conditions — that results in interference with normal daytime functioning.

There are three types of insomnia: transient, short-term, and chronic. Transient insomnia lasts one week or less. Short-term insomnia lasts from one to four weeks. Chronic insomnia is defined as occurring nightly for more than six months and is frequently accompanied by precipitating or contributing factors, which range from temporary but significant life events to long-term potentially significant medical or psychiatric conditions.<sup>1</sup>

The focus of this article is the condition of chronic insomnia, its available remedies, and associated research-based efficacy and cautions.

Chronic insomnia affects 58 percent of the adult population at some point in their lives.<sup>2</sup> It occurs more frequently in women, older adults, and patients with chronic medical and psychiatric disorders. The combination of inadequate identification and inadequate treatment of chronic insomnia has significant implications for an individual’s quality of life and economic productivity, and for the general public health. Chronic insomnia can impair an individual’s daily personal and work life. It is associated with increased health-care usage and costs, including twice as many hospitalizations and physician visits.<sup>3</sup> Insomnia is also a risk factor for a number of serious disorders, such as depression, and can be an important indicator or symptom of other medical and psychiatric disorders.

Chronic insomnia is classified as primary or secondary. The pathogenesis of primary insomnia is not clearly understood, unlike that of insomnia that is secondary to other causes. Some critical medical conditions often associated with secondary chronic insomnia are chronic pain syndromes, coronary heart disease, asthma, gastrointestinal disorders, vascular disorders, chronic fatigue, and endocrine and metabolic disorders.

Depression, anxiety, stressful events, and poor sleep habits can precipitate episodes of insomnia. Approximately 40 percent of adults with chronic insomnia have a diagnosable psychiatric disorder. In literature discussing the relationship between insomnia and depression, it is noted that either condition has potential to initiate the other.

Certain medications and substances, including caffeine and alcohol, theophylline, steroids, antihypertensives, and antidepressants can trigger or exacerbate insomnia.

A thorough medical evaluation is necessary to discover, manage, and attempt to eliminate the root cause of chronic insomnia. Possible treatment options for secondary insomnia include cognitive behavioral therapy,

over-the-counter products, and prescription medications — both with and without FDA approval as treatment for insomnia.

**FDA-APPROVED PRESCRIPTION MEDICATIONS**

FDA-approved products for the treatment of insomnia are divided into two classes: benzodiazepine hypnotics and non-benzodiazepine hypnotics. Both classes of drugs act on the benzodiazepine receptor with different affinities for various subtypes of the receptor. They have an effect on the neurotransmitter, GABA (gamma-aminobutyric acid), which is involved in the initiation of sleep. There is one exception to this mechanism of action: ramelteon, a melatonin receptor agonist which is the only FDA-approved insomnia treatment drug that is not a controlled substance.

**Benzodiazepine hypnotics**

In the benzodiazepine hypnotic class, double-blind, placebo-controlled trials have demonstrated efficacy for the treatment of insomnia.<sup>4</sup> These trials have typically been short-term (four to six weeks). Longer-term use (four to eight weeks) was associated with reduced effect or tolerance. Because of their longer half-life, these medications are generally more effective for maintaining sleep. The longer half-life also contributes to higher rates of next-day impairments, such as morning sedation, cognitive impairment, and problems with motor coordination.

The products with the longest half-life, flurazepam and quazepam, should be avoided in the elderly due to risk of falls. Because of possible abuse liability, the FDA has indicated that the use of flurazepam and quazepam should be limited to seven to ten days, with reevaluation if used for more than two to three weeks.

<b>EXHIBIT 1</b>	
<b>BENZODIAZEPINE HYPNOTICS APPROVED FOR THE SHORT-TERM TREATMENT OF INSOMNIA</b>	
	Estazolam
	Flurazepam
	Quazepam
	Temazepam
	Triazolam

Withdrawal effects, especially rebound insomnia, are generally rare with longer-acting agents. Withdrawal effects are significant, however, with the use of temazepam, the most commonly prescribed product in this class. Triazolam and estazolam have the potential for drug interactions when administered in combination with other drugs that are metabolized by the Cytochrome P450 system.

For the reasons stated above, long-acting benzodiazepines should be avoided in the elderly. Use of non-benzodiazepine hypnotics should be considered in this patient population due to improved safety and side-effect profiles. These medications, especially Roserem, have a very low risk of residual daytime motor and cognitive effects. Roserem has the added benefit of not being a controlled substance.

If a shorter acting benzodiazepine is used in any patient population longer than four to eight weeks, it is important to monitor for diminishing effects. Countering diminishing effects by increasing the dose, however, could negate the benefits of a short-term medication. Switching to a non-benzodiazepine hypnotic, with improved-safety and reduced-dependency profiles, would be a better treatment option. There are three medications within this class that do not have a specified treatment duration. They are mentioned below.

If long-term use of a benzodiazepine is part of a patient's medication profile and discontinuation is required, a monitored, gradual withdrawal of the medication would be necessary. An article published in *Drug Therapy Perspectives* suggested the following management guidelines:<sup>5</sup>

- before attempting treatment discontinuation, assess patient for anxiety and/or depression and treat accordingly;
- individualize withdrawal regimen;
- explain the withdrawal program to the patient;
- aim for withdrawal over eight to twelve weeks;
- reduce dose in steps of about one-eighth (or within a range of one-tenth to one-quarter) every two weeks;
- if withdrawal symptoms occur, maintain dose until symptoms improve then reduce dose further (if necessary, in smaller biweekly steps);
- give plenty of support and monitor progress frequently; and
- if tapering regimen fails, try substitution with zopiclone or zolpidem.

The last suggestion was discussed in relation to minimizing rebound insomnia. Benzodiazepines can alter sleep patterns, but zolpidem and zopiclone

do not. A study was completed in 134 long-term benzodiazepine users. In the study, zopiclone was administered one of three ways: an abrupt switch from the benzodiazepine, after a drug free interval, or as an overlapping regimen. Zopiclone improved both sleep and daytime alertness. After one to two months, zopiclone was withdrawn. One year to one and one-half years later, over 80 percent of patients remained off hypnotics.

Another article published in the *American Journal of Psychiatry* concluded that both cognitive behavioral therapy and a tapered medication program by themselves can help improve sleep and reduce insomnia in older adults with insomnia, but the combination of the two therapies produces a synergistic effect. Psychological treatment can support success and help reduce negative feelings and anxiety that can result from impaired sleep.

### Non-benzodiazepine hypnotics

Non-benzodiazepine hypnotics are a relatively new class of products. They tend to have shorter half-lives and quicker onset of action than the benzodiazepines, which makes them generally more effective for sleep initiation than sleep maintenance. They tend to have minimal morning sedation and daytime cognitive effects and are considered to have a lower potential for abuse than benzodiazepines.

Zaleplon and zolpidem tartrate are indicated for short-term use (7 to 10 days) due to lack of studies to support effectiveness with longer use. However, zolpidem tartrate and zaleplon are routinely prescribed for long-term use.

Treatment durations are not specified for eszopiclone, ramelteon, or zolpidem tartrate extended release. Studies are nonexistent for use beyond six months for any of the medications in this class except eszopiclone. Six-month studies of eszopiclone indicate no signs of tolerance or problems with tolerability.<sup>7</sup> A recent study cited by the National Institute of Health conference indicates efficacy and safety with minimal tolerance or abuse liability for over 12 months of use. The most commonly reported side effect with eszopiclone is a bitter taste.

Withdrawal effects are minimal with zolpidem tartrate and nonexistent with zaleplon. However, rebound insomnia is a potential problem with all hypnotics. Amnesia and effects on memory are rare, although amnesia, including sleep-related eating, has been reported with the use of zolpidem tartrate. Due to its unique mechanism of action, ramelteon may be less likely to cause impaired memory and body movement function effects. This may make it a better choice for the elderly population. Because zolpidem tartrate extended release and eszopiclone have a longer duration of action,

they may be useful for patients who have trouble staying asleep. Zaleplon and ramelteon have a quicker onset and shorter duration of action and may be more useful for patients who have difficulty falling asleep. Zolpidem tartrate has an onset similar to zaleplon's, but with a longer duration and has the potential to be useful for patients that have difficulty with both falling and staying asleep.

With the exception of ramelteon, non-benzodiazepine medications should be taken immediately before going to bed due to rapid onset of action. Ramelteon should be taken 30 minutes before bedtime. Eszopiclone is metabolized by the Cytochrome P450 system and should be monitored for interactions when used in combination with other drugs that are metabolized by this system. Zolpidem tartrate is now available in a generic form and could provide a cost savings for the right patient selection. In general, the non-benzodiazepine class of medications is considered safer than the benzodiazepine hypnotics.

Withdrawal effects and rebound insomnia are very rare with the non-benzodiazepine class of medications, unlike the benzodiazepine class. If discontinuation is suggested, a dose reduction may mitigate any risks. It should be noted that there is sparse data on this topic.

**PRESCRIPTION MEDICATIONS WITHOUT FDA APPROVAL TO TREAT INSOMNIA**

Some sedating antidepressants, antipsychotics, and anticonvulsants are prescribed to treat chronic insomnia. There is some speculation that their potentially lower cost, lack of long-term use restrictions, and low abuse potential makes them an attractive choice.

Trazodone, a tricyclic antidepressant, is one of the most commonly prescribed medications for chronic insomnia. There is a small amount of data to support its efficacy, but no data on long-term use. In a comparative

study, Trazodone was found to be less effective than zolpidem tartrate. In addition, Trazodone can produce significant anticholinergic side effects, such as orthostatic hypotension, blurred vision, nausea, dry mouth, constipation, drowsiness, and headache. There is also a risk of falls in the elderly; thus, it should be used with caution in this population. Risks are minimized with lower doses. Another antidepressant, Doxepin, was studied in a four-week trial. Results included significant improvements in sleep initiation, duration, and quality.

Antipsychotics and anticonvulsants can have serious side effects, incur significant risks, and have little to no data supporting their efficacy in treating insomnia. These medications are not recommended for the treatment of insomnia unless a direct diagnosis is also present to warrant their use.

**OVER-THE-COUNTER MEDICATIONS**

Antihistamines, such as diphenhydramine, are the most commonly used over-the-counter (OTC) insomnia remedies. Random controlled trials suggest that they improve sleep subjectively, but conclusive objective evidence is lacking. Morning sedation is a recognized side effect. Another negative of antihistamine use is the potential for anticholinergic side effects, such as constipation, dry mouth, urinary retention, and blurred vision.

Melatonin, with various doses, has been studied with small numbers of patients treated for short periods. Results of these studies are conflicting. Melatonin does appear to be effective for the treatment of jet lag. OTC melatonin is unregulated, and preparations may vary. The American Sleep Disorder Association considers melatonin to be an experimental drug and does not recommend its use without medical supervision.<sup>8</sup> More substantial long-term studies are needed to support the use of melatonin.

There is no evidence of adequate research related to alternative herbal treatments.

**SUMMARY**

- Chronic pain conditions are risk factors for chronic insomnia.
- Off-label prescribing with regard to treatment duration is common.
- The non-benzodiazepine class of hypnotics provides a potentially safer alternative to the benzodiazepine class.
- To date, clinical studies to support the long-term use of any medication to treat chronic insomnia are unavailable. It is necessary to rely on case-by-case clinical judgment for appropriate management.
- Based on review of the literature, there is an obvious need for more

EXHIBIT 2 NON-BENZODIAZEPINE HYPNOTICS APPROVED FOR THE TREATMENT OF INSOMNIA	
Zaleplon	short-term treatment
Zolpidem	short-term treatment
Eszopiclone	not limited to short-term treatment
Zolpidem CR	not limited to short-term treatment
Ramelteon	not limited to short-term treatment

quality, long-term studies to assess the effectiveness and safety of drugs for the treatment of chronic insomnia.

- Much of the existing data is derived from studies of short-term use. However, one-third of Americans consider insomnia to be a long-term problem for them.<sup>9</sup>
- Responsible decisions regarding medication choices incorporate the following:
  - assessment of the nature of the chronic insomnia;
  - elimination or management of underlying conditions and risk factors;
  - selection of the appropriate agent based on half-life and sleep patterns;
  - evaluation of concomitant drug use;
  - consideration of the patient profile in conjunction with potential side effects;
  - monitoring at appropriate intervals for possible adverse events and side effects; and
  - ongoing assessment of continued efficacy.

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