



Insomnia Related to Menopause

Insomnia Prevalence

Insomnia is characterized by self reports of difficulty falling asleep or maintaining sleep and/or unrestorative sleep that is accompanied by daytime symptoms such as sleepiness, irritability, or cognitive impairment. About one-third of adults in the U.S. experience occasional insomnia and 10 to 15 percent suffer from it chronically.¹ The prevalence of insomnia in the primary care population is even higher, possibly due to high rates of concomitant illnesses.²

Groups Most at Risk of Developing Insomnia

Women are at higher risk of insomnia than men.³ The specific factors that increase the risk of insomnia among women are unclear, but evidence suggests that female reproductive biology may contribute to insomnia throughout the life span. The higher prevalence of insomnia in women may also be explained by higher rates of depression, which is strongly associated with insomnia, among women. Psychosocial factors and having the dual responsibility of career and caregiver/homemaker may also increase the risk of insomnia in women.

Insomnia prevalence increases with age. The most common insomnia complaint among older adults is difficulty maintaining sleep, though many older adults experience a variety of insomnia symptoms as they age. For example, sleep efficiency decreases, sleep latency increases, and older adults experience more frequent nocturnal awakenings.⁴ Not all older adults sleep poorly; epidemiological evidence suggests that insomnia prevalence among older adults is between 20 and 40 percent.⁵

Insomnia Comorbid with Medical and Psychiatric Illness

Among older adults, insomnia is often comorbid with medical illnesses such as rheumatoid arthritis, Parkinson's disease, congestive heart failure, stroke, asthma, chronic obstructive pulmonary disease, and cancer.⁶ In addition, medications used to treat such conditions may cause nighttime insomnia or daytime drowsiness, which can further disrupt the sleep cycle. Chronic pain is also contributory to insomnia in older adults. In many cases, effectively treating or managing the medical condition is enough to resolve the sleep problem.

Insomnia is common in patients with psychiatric disorders, particularly depression.⁷ The relationship between insomnia and depression is complex and multidirectional; insomnia may be a symptom of depression, a predisposing factor for it or the two conditions may have parallel etiology.^{8 9} Depressed patients may suffer from a range of insomnia symptoms, including difficulty falling asleep (sleep onset insomnia), difficulty staying asleep (sleep maintenance insomnia), unrefreshing sleep, and daytime sleepiness. Research suggests that the risk of developing depression is highest among people with both sleep onset and sleep maintenance insomnia.¹⁰

Insomnia Comorbid with Other Sleep Disorders

Insomnia in older adults may also be comorbid with other sleep disorders, including restless legs syndrome (RLS) and obstructive sleep apnea (OSA). Symptoms of RLS and OSA may cause extreme daytime sleepiness, irritability, and repeated nocturnal awakenings that are sometimes mistaken for insomnia. OSA is more common in post-menopausal women than in women who have not gone through menopause.¹¹ Patients who complain of insomnia as well as snoring and daytime sleepiness should be screened for OSA.

Sleep problems such as RLS and OSA may also contribute to poor sleep in the patient's bed partner. For example, one member of a couple may suffer from insomnia related to the other's snoring. Additionally, sleep problems may also cause significant daytime fatigue and irritability that can impact a marriage or other relationship. For patients with sleep problems, it is generally helpful to interview the bed partner, especially since the patient may not be aware of his or her sleep symptoms.

Short Sleep is a Risk Factor for Weight Gain

A number of recent population-based studies indicate that short sleep is associated with weight gain and obesity.¹² Patients with sleep disorders commonly complain of low energy and a lack of desire to exercise. Such factors may contribute to weight gain, but physiological factors may also be contributory. For example, upregulation of appetite has been shown to occur in response to short sleep durations. Data from a 2004 study by researchers at the University of Chicago showed that in response to sleep restriction, healthy male subjects experienced an increase in the hormone ghrelin and a decrease in the hormone leptin, which corresponded with an increase in hunger and appetite, especially for high-calorie, high-carbohydrate foods.¹³ The association between sleep and weight may be bi-directional: sleep loss contributes to weight gain and weight gain exacerbates sleep problems, especially OSA and other forms of sleep-disordered breathing.

Insomnia Related to Lifestyle Factors

A patient's lifestyle and daily habits may also contribute significantly to sleep problems. Alcohol is a common self-treatment for insomnia, especially for sleep onset insomnia. However, alcohol causes shallow and fragmented sleep throughout the night and may lead to dependency and abuse.¹⁴ Excessive caffeine consumption is another common cause of disturbed sleep. Patients who have difficulty initiating sleep at night should be advised to limit or avoid caffeine in the second half of the day.

Stressful life events may also cause insomnia. One study found that people with chronic insomnia experience a greater number of stressful life events during the year of insomnia onset compared with other years and compared with good sleepers.¹⁵ In cases where the stressful life event is short-lived, sleep problems usually resolve once the stressor is resolved.

Insomnia Related to Menopause

Symptoms of menopause such as hot flashes and night sweats may contribute to poor sleep in middle-aged women, as can depression and sleep disordered breathing.¹⁶ Treatment of insomnia related to menopause should focus on sleep hygiene and behavioral therapies and may include hormone replacement therapy and treatment with insomnia medications (see treatment sections).¹⁷ Evidence suggests that treating menopause symptoms can significantly improve sleep quality and minimize the adverse effects of insomnia.¹⁸

Sleep Hygiene

Treatment for insomnia begins with sleep hygiene, which involves adopting habits that promote sleep and alertness, including:

- Keeping a regular sleep/wake schedule
- Having a relaxing bedtime routine
- Avoiding caffeine and alcohol
- Creating a sleep environment that is cool, dark, quiet, and comfortable

Sleep hygiene and behavioral remedies are usually employed before the use of medications. However, pharmacological therapies may also be a first-line treatment in patients with more severe insomnia, which generally refers to sleep difficulty that occurs every night and causes significant daytime impairment.¹⁹ When used alone, behavioral strategies have been shown to be an effective long-term treatment for insomnia.²⁰ However, evidence suggests that pharmacological therapies used in combination with behavioral strategies are more effective at treating short-term sleep difficulties than behavioral strategies alone.²¹

Behavioral/Psychological Therapies

Behavioral and/or psychological therapy for insomnia focuses on addressing the maladaptive beliefs that perpetuate sleep difficulty, including feelings of hopelessness about one's ability to achieve healthy sleep and the belief that needing a full night's sleep is a sign of weakness. Such beliefs may confound behavioral therapies for insomnia, especially when it is comorbid with depression.²² Behavioral treatments such as cognitive restructuring that target these beliefs may improve patient outcomes.

In recent years, cognitive behavioral therapy (CBT) for insomnia has become increasingly popular. CBT for insomnia has been shown to produce significant and lasting improvements in all measures of insomnia with no side effects or risk of dependency.²³ It is also generally less expensive than pharmacological therapy.²⁴ CBT for insomnia typically requires multiple sessions with a practitioner over a period of six to eight weeks, though research suggests that even brief behavioral interventions can significantly improve insomnia as well as daytime symptoms of sleepiness and anxiety.²⁵ Research also suggests that as many as one-third of insomnia patients become good sleepers as a result of CBT for insomnia.²⁶

Behavioral/Psychological Therapies, cont'd

Cognitive behavioral therapy (CBT) for insomnia typically consists of the following components, and practitioners may use one or a combination of them:

- Cognitive restructuring - targets the patient's maladaptive beliefs about sleep, such as excessive worry about the effects of not sleeping.
- Sleep restriction – limits the patient's time in bed to the amount of time he or she typically sleeps, and then gradually increases time in bed as sleep time increases.
- Stimulus control – allows the patient to re-associate the bedroom with sleep. It involves going to bed only when sleepy, limiting the bedroom activities to sleep and sex, getting out of bed if sleep is not achieved within 15 minutes and avoiding naps.
- Relaxation therapy – reduces stress and anxiety, relaxes the body, and prepares the patient for sleep.

For specific guidelines on behavioral interventions, see Chesson et al, 1999.

Pharmacological Therapies

Pharmacological treatments are recommended for patients in whom behavioral strategies alone are not effective. There are currently ten drugs with approval by the U.S. Food and Drug Administration (FDA) for the treatment of insomnia (see Table 1), and all are recommended for short-term use. Those that have received FDA approval since 2005 (ramelteon, eszopiclone and zolpidem CR) may be prescribed without limitation on the duration of their use.

Table 1 – FDA-Approved Medications for the Treatment of Insomnia

Drug	Chemical Class	Recommended Dose in Adults, in Older Adults	Half Life (hours)
Estazolam	Benzodiazepine	2 mg, 1 mg	8 - 24
Eszopiclone	Non-benzodiazepine	2 mg, 3 mg, 1 mg	5 - 7
Flurazepam	Benzodiazepine	30 mg, 15 mg	48 - 120
Quazepam	Benzodiazepine	15 mg, 7.5 mg	48 - 120
Temazepam	Benzodiazepine	30 mg, 15 mg	8 - 20
Triazolam	Benzodiazepine	0.25 mg, 0.125 mg	2 - 4
Zaleplon	Non-benzodiazepine	10 mg, 5 mg	~1.0
Zolpidem	Non-benzodiazepine	10 mg, 5 mg	1.5 – 2.4
Zolpidem CR	Non-benzodiazepine	12.5 mg, 6.25 mg	6.26 – 12.5
Ramelteon	Melatonin agonist	8 mg, 8 mg	1.5 - 5

Pharmacological Therapies for Insomnia, cont'd

The mechanism of action of most hypnotics is via modulation of the GABA-A receptor complex. Hypnotic medications fall into two major categories: the benzodiazepines (temazepam, flurazepam, and triazolam) and the newer non-benzodiazepines (zaleplon, zolpidem, zolpidem MR and eszopiclone). Ramelteon helps promote sleep via a different mechanism of action, namely as a melatonin receptor agonist. Good efficacy, together with improved safety and tolerability of these newer agents, has made them the first line choices when a hypnotic medication is indicated.

Although long-term studies of up to 12 months are available for these newer hypnotic medications, more are needed in older adults. Furthermore, clinical practice guidelines for the treatment of chronic insomnia in older adults are lacking. With the advancement of our knowledge of the science of sleep and the fact that insomnia is a chronic condition that often times require long-term management, studies of long-term efficacy and safety will allow us to develop evidence-based clinical guidelines for the safe and effective treatment of insomnia in older adult populations.

Pharmacological Treatments – Potential for Side Effects

Each of the medications approved for the treatment of insomnia has the potential for adverse effects, which may include daytime drowsiness, cognitive impairment, ataxia, dependence, and rebound insomnia. Research suggests that the occurrence of these effects may be lower with the newer sleep medications (e.g., ramelteon, eszopiclone, and zolpidem CR), most likely because these agents have shorter half-lives.²⁷ Additionally, the FDA recently requested that manufacturers of insomnia medications revise their product labels to include stronger language concerning potential risks. These risks include severe allergic reactions and complex sleep-related behaviors, which may include sleep driving. Sleep driving is defined as driving while not fully awake after ingestion of a sedative-hypnotic product, with no memory of the event.

The Effect of Pharmacological Therapy on Sleep Apnea

Hypnotic medications, particularly the older agents, have the potential to suppress respiratory function in patients with obstructive sleep apnea (OSA). As of this writing, zolpidem and zaleplon have been studied in patients with insomnia and sleep apnea treated with nasal CPAP only. There is evidence that in patients with insomnia, zolpidem may improve compliance with nasal CPAP.²⁸ Ramelteon has been studied in patients with mild to moderate untreated sleep apnea and did not worsen oxygen saturation.²⁹ More recently, a pilot study using eszopiclone also demonstrated no significant effect on apnea level or oxygen saturation in patients with mild to moderate obstructive sleep apnea.³⁰

Off-Label and Over-the-Counter Medications

There are a number of prescription drugs without FDA approval for insomnia that are widely prescribed to treat insomnia, including sedating antidepressants, antipsychotics and antihistamines.³¹ Antihistamines and other over-the-counter medications are also commonly used for the treatment of insomnia. However, the effectiveness of these products for the long-term treatment of insomnia has not been supported by randomized clinical trials and many have potentially serious side effects. Thus, they are not recommended for the treatment of insomnia.

Pharmacological Considerations for Insomnia Comorbid with Depression

Treatment for insomnia may be complicated by comorbid depression. Because insomnia and depression commonly coexist, patients with both conditions are often treated with sedating antidepressant medications. In fact, the antidepressant trazodone is now the most commonly prescribed medication for insomnia.³² In the short-term, evidence suggests that sedating antidepressants improve symptoms of insomnia. However, sedating antidepressants carry a risk of side effects such as residual sedation, weight gain and interaction with other medications as well as cognitive, psychomotor, and cardiovascular side effects. The potential benefits of sedating antidepressants should be evaluated by practitioners against the potential for adverse effects. It is important to keep in mind that treating comorbid depression or any other comorbid condition may not resolve a patient's insomnia. Rather, insomnia treatment may need to be considered separately or in combination with therapies for the comorbid condition.

The Case of the Middle-Aged Woman

Presentation and Sleep Complaints

"AM" is 55 year old woman who presents to a primary care physician with complaints of sleeplessness and sleepiness for approximately eight months. Initially, she only had difficulty falling asleep two to three nights per week. However, over the past five months, sleep and daytime fatigue have increased in severity and frequency. She now wakes up three or more times per night at least five nights per week. She has tried to maintain an active social and professional life. She was the executive director of a nonprofit organization, and for the past year has worked from home as a consultant. She notes increased irritability and lack of motivation.

She has always been a poor sleeper during times of stress, but nearly always improved after a few days. She occasionally takes over-the-counter medications. She also notes an increase in caffeine intake (four cups of coffee and one to three diet colas per day) just to stay awake in the afternoon. When asked, she attributes her insomnia to a combination of an inability to relax and hot flashes.

Medical and Social History

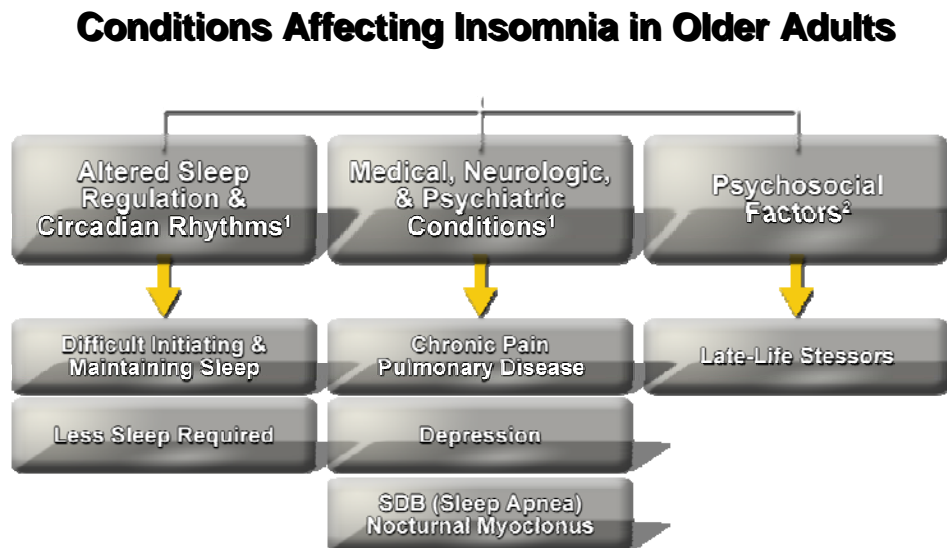
AM's medical history includes hypertension, gastroesophageal reflux, arthritis in the knee and a mild stroke (arm weakness and slurring of speech that lasted a few hours) about five years ago. She has not experienced recurrent symptoms since. She had a bout of depression in her 30's associated with a miscarriage. Her medications include atenolol, hydrochlorothiazide, diphenhydramine for sleep, and acetaminophen and ibuprofen for knee pain. She has 2 glasses of wine most days of the week with dinner, and has never smoked cigarettes. Her husband complained that he, too, was sleeping poorly because he was disturbed by her restlessness. She is married with 2 children who are both in college. Of note is that her mother had breast cancer.

Due to fatigue, AM has been unable to exercise which has increased her pain and has caused her to gain more than 15 pounds during the past six months. She has been postmenopausal since age 53. She was on hormone therapy until last year, when she stopped because of concerns of breast cancer and stroke risks.

Differential Diagnosis

The patient was diagnosed with insomnia and was educated regarding good sleep hygiene and specifically advised to maintain a regular sleep/wake cycle, decrease her caffeine intake, resume regular exercise, but not within three hours of bedtime, and avoid alcohol with dinner. See Figure 1 for a review of the multiple factors that contribute to insomnia in older adults.

Figure 1 – Conditions Affecting Insomnia in Older Adults



¹Barthlen GM. *Geriatrics*. 2002;57:34-39.

²Ancoli-Israel S, et al. *J Am Geriatr Soc*. 2005;53(suppl):S264-S271.

First Follow-up with Primary Care Physician

At her first follow-up visit, AM said that although she has increased her exercise (swimming) level to three times per week and has tried to adhere to the sleep hygiene instructions, she notes only some improvement in her ability to fall asleep. She continues to wake up several times during the night and remains tired during the day. She continues to take over-the-counter medications to help her fall asleep a few times

per week, but they tend to produce a “hung over” effect. She states that she really needs some help for her sleep. She reports being irritable, no longer enjoying time with her friends, and getting into more arguments with her husband. Just last week, she broke down in tears because her husband came home late for dinner. AM's symptoms suggest depression. She was prescribed paroxetine and zolpidem as needed. In addition, she was advised to consult a psychiatrist for further evaluation.

Second Follow-up with Primary Care Physician

After two months, AM returned to her primary care doctor complaining of continued difficulty with sleep and increased irritability due to lack of sleep. She had not seen a psychiatrist yet. She feels less anxious and somewhat less irritable on the SSRI, paroxetine. Her mood has improved. Zolpidem helped her get a few more hours of sleep, but she remains tired. She continues to wake up during the night and has some difficulty falling asleep. She also gained six to eight pounds during the past two months. Her primary care physician increased the dose of paroxetine to 20 mg and refilled zolpidem. The patient does not wish to see a psychiatrist because she thinks that the problem is her sleep and she has very limited mental health insurance coverage. Her PCP referred her to a sleep specialist for further evaluation.

Evaluation with a Sleep Specialist

During her evaluation with a sleep specialist, AM explained that although she was most bothered by the nighttime awakenings as well as daytime symptoms such as lack of concentration and fatigue. When asked, she admitted that she has been snoring for the past six months. She reported that her husband complained of her snoring, but did not say that she stopped breathing. She denied uncomfortable sensations in the legs. She did not think that pain was keeping her awake. Her arthritis is mild and she can manage with ibuprofen a few times per week.

Examination of the upper airway was normal, except for retrognathia. The remainder of her physical examination was normal. The sleep specialist had her complete an Epworth Sleepiness Scale (ESS) to evaluate her level of sleepiness. The patient's ESS score was 12. A score of ten or above indicates excessive sleepiness and suggests that medical evaluation may be appropriate.

The sleep specialist recommended that the patient maintain a sleep diary for 14 days and return for reassessment in two weeks. Her sleep diary showed an average 5.5 hours of sleep each night, with awakenings on 12/14 nights between 2:00 and 4:30 am lasting 10-30 minutes. She consumed two cups of coffee in the morning and two cans of soda in the afternoon and one cup of tea with dinner. In addition to a glass of wine, she admitted to having one to two after-dinner drinks to help her sleep. The sleep specialist advised her against drinking more than one glass of wine or beer with dinner. He reinforced healthy sleep practices such as maintaining a regular sleep schedule throughout the week, avoiding caffeine after 10:00 am, and increasing time outdoors for exercise and exposure to light. He emphasized that avoiding naps was necessary to increase the drive for sleep later at night.

The sleep physician explained sleep restriction therapy, which is designed to limit time in bed when not sleeping in order to promote sleep efficiency (time asleep/time in bed). AM reports spending approximately eight hours a day in bed, but only four to five hours sleeping—a pattern that may cause poor sleep efficiency. Her physician restricted her time in bed to only six hours by suggesting she go to bed at midnight and maintain a regular wake time. Over the subsequent few weeks, as AM's sleep time increased, her physician recommended continuing to increase time in bed to 8 hours.

Since her sleep study, she has tried to taper zolpidem. She only uses it intermittently when she has difficulty falling asleep. Because of her snoring and daytime sleepiness, AM was also referred for polysomnography (PSG), the results of which indicated mild obstructive sleep apnea. Additional PSG findings include:

Polysomnographic Results:

- Sleep onset latency: 32 minutes (<20 minutes is normal)
- Total sleep time: 356 minutes
- Sleep efficiency: 75% (>90% is normal)
- Alpha wave intrusions: nonspecific finding-associated with non-restorative sleep)
- Periodic limb movements index: 3.6 (<5 is normal)
- Apnea/hypopnea index: 7.5 (<5 is normal)

AM was prescribed continuous positive airway pressure (CPAP) to treat her OSA. However, a CPAP titration study showed poor tolerance and decreased sleep efficiency compared to the baseline night. She has tried multiple masks but could not sleep with the apparatus. AM was also fitted for an oral appliance, which she reported using intermittently. At a one-month follow-up with the sleep specialist, she reported improved sleep (averaging about 6.5 hours) and improved mood. However, she continues to feel unrefreshed and sleepy during the day, despite improvement of insomnia.

Second Follow-up with Primary Care Physician

Six weeks later, AM visited her PCP, who reviewed the recommendation of the sleep consultant, the results of the overnight sleep study, and her progress with oral appliance therapy. The PCP consulted with the sleep specialist who felt that the very mild number of respiratory events may be “within normal range” for the age of the patient and did not think that surgical intervention was necessary. AM requested a hypnotic medication because of her continued problems with sleep. The PCP encouraged behavioral therapies and continued therapy for depression and insomnia with an SSRI and a hypnotic medication. He had explained that if she did not improve sufficiently that other medications may be tried. The patient did not want to re-start HT because of her concerns regarding breast cancer.

Summary

Insomnia etiology in postmenopausal women is often multifactorial and comorbid with an age-related increase in chronic medical and psychiatric conditions. Recognition of this fact is essential to evaluation and subsequent treatment. In older adults, medical disorders, neurological disorders, medications, mood disorders, other sleep disorders and life style factors should be considered in a differential diagnosis. In addition to the patient’s own sleep habits, it is important to inquire about the bed partner’s snoring or movements during sleep which in turn can disturb the patient’s sleep. A sleep diary used for two weeks or more can provide a more detailed assessment of sleep and wake behavior and aid in behavioral treatments, such as sleep restriction therapy. When a diagnosis of sleep apnea is suspected, an overnight sleep study is a useful diagnostic tool. For patients with sleep apnea, the most commonly used medical treatment is nasal continuous positive airway pressure (CPAP), though oral appliance therapy is an option for patients who do not tolerate CPAP.

The general approach to long-term insomnia management includes sleep hygiene education, cognitive behavioral therapy, and pharmacological approaches. Behavioral therapy alone, or when combined with pharmacologic treatments, have been shown to be effective for primary as well as comorbid insomnia.³³ Therefore, behavioral strategies should be an integral part of the management of insomnia. There is also evidence that pharmacotherapy, when used in combination with behavioral approaches can produce short term benefits over behavioral therapy alone.³⁴



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