**Last Section Update:** 08/2025

**Contributor(s)**: **Shayna Sandhaus**, PhD; **Maureen Williams**, ND

## Table of Contents

Start



## 1 Overview

### Summary and Quick Facts About Insomnia

- An estimated 10% of the global population experience chronic insomnia and more than 30% report sleep difficulties.
- In this protocol, you will learn about pharmaceutical sleep aids and the risks associated with their use. The efficacy and safety of several emerging therapies will also be discussed.
- Simple lifestyle strategies and nutrient supplements can improve sleep and help relieve insomnia.
- Melatonin plays a critical role in regulating sleep-wake cycles. Supplementation, at appropriate doses and with correct timing, has been shown to reduce insomnia symptoms in randomized controlled trials.

### What Is Insomnia?

Insomnia is a common sleep disorder affecting approximately 10% of Americans. Insomnia can involve the inability to fall asleep (onset insomnia) or stay asleep (maintenance insomnia). Sleep deficiency not only diminishes quality of life, but it also increases risks of multiple health problems, such as anxiety, cardiovascular

disease, and obesity.

Short-term insomnia can last several days or weeks, often in response to a stressful life event. Chronic insomnia, which lasts for three months or longer and affects sleep on three or more nights per week, can have profound long-term effects on health. Insomnia may arise without any clear underlying cause or may be related to a co-existing condition or medication.

Several natural interventions, such as **melatonin** and **valerian**, may help improve sleep and restore the body's natural circadian rhythm.

### What Are Causes and Risk Factors of Insomnia?

- Female gender—hormonal shifts from menstruation, pregnancy, and menopause can contribute to sleeping problems
- Advanced age
- Mental health problems, such as anxiety, depression, and bipolar disorder
- Physical health conditions, such as cardiovascular, urinary tract, and respiratory conditions
- Certain medications, such as decongestants, chemotherapy drugs, and beta-agonists
- Excess stress levels
- Irregular sleep habits, such as due to shift work

### What Lifestyle and Non-Pharmacological Changes Can Be Beneficial for Insomnia?

- Improving "sleep hygiene"
  - Minimize light and noise
  - Avoid large meals before bedtime
  - Avoid bedtime activities not related to sleep
- Sleep restriction therapy, which limits the amount of time spent in bed
- Cognitive-behavioral therapy
- Relaxation therapies

### What are Conventional Medical Treatments for Insomnia?

- Over-the-counter drugs, such as antihistamines for occasional use
- Benzodiazepines, such as alprazolam (Xanax), clonazepam (Klonipin), and diazepam (Valium) for short-term use
- Benzodiazepine-like drugs, such as zaleplon (Sonata), zolpidem (Ambien), and eszopiclone (Lunesta) for short-term use
- Antidepressants with sedative properties, such as doxepin (Silenor), trazodone (Desyrel), and amitriptyline (Elavil)

### What Are Novel and Emerging Therapies for Insomnia?

- Dual orexin receptor antagonists like suvorexant (Belsomra) promote sleep by blocking wakefulness-promoting neuropeptides from binding to their receptors.
- Drugs that target melatonin receptors (MT1 and MT2), such as ramelteon (Rozerem), may induce sleep by mimicking melatonin.
- 5-HT2 serotonin receptor antagonists may increase deep sleep.
- Short-term use of the anesthetic drug propofol may help reset sleep rhythms.

### What Natural Interventions May Be Beneficial for Insomnia?

- **Melatonin**. Melatonin is a hormone that is highly correlated with the body's sleep-wake cycle. Low melatonin levels have been linked to insomnia in the elderly. Supplementation may help improve sleep.
- **L-tryptophan**. L-tryptophan is a precursor to melatonin and serotonin. Supplementation with L-tryptophan may increase melatonin production to aid sleep and may help alleviate some forms of depression.
- **Magnesium**. Magnesium helps regulate the body's circadian rhythm. A study showed supplementation with magnesium, zinc, and melatonin improved sleep in elderly subjects.
- **Zinc**. Higher zinc levels in the body may be correlated with longer periods of sleep. Oral administration of

zinc can improve sleep quality and duration.

- **Valerian**. Valerian is a sedative herb that has been used since ancient times to treat insomnia. A study comparing valerian supplementation to a commonly prescribed tranquilizer found comparable efficacy.
- **Ashwagandha**. Ashwagandha is an herb shown in several animal models to reduce stress and anxiety and improve sleep. Human trials indicate ashwagandha may decrease stress and anxiety, but further research is needed.
- **Lemon balm**. Lemon balm has been shown to improve mood and feelings of calmness. Lemon balm, alone or in combination with valerian, may also improve sleep and symptoms of insomnia.
- **Lavender**. Aromatherapy with lavender essential oil may improve sleep quality and reduce feelings of drowsiness after waking.
- **Natural interventions** that promote relaxation. These include honokiol, glycine, chamomile, passion flower, and bioactive milk peptides.
- **Nutrients that reduce nocturia** (the need to urinate at night). These include beta-sitosterol, lycopene, *Pygeum africanum*, *Lindera aggregata*, *Crataeva nurvala*, and *Equisetum arvense*.

## 2 Introduction

Insomnia is defined as difficulty falling or staying asleep, dissatisfaction with sleep, and daytime impairment due to sleep loss.[1] Worldwide, about 10% of people have chronic insomnia and more than 33% report getting insufficient sleep.[2] Roughly 20% of Americans reportedly experience occasional insomnia and another 10% struggle with an insomnia disorder.[3] People with medical, psychiatric, and substance use disorders, as well as the elderly, women, and those in low-income households, are especially prone to insomnia.[1]

Observational research shows seven to eight hours of sleep per night is optimal for health.[4] Sleep is essential for learning and memory formation, emotional well-being, physical growth and development, immune function, and cardiovascular health. Sleep is also integral to cellular repair processes, helps regulate insulin levels, and normalizes appetite signaling. Sleep deficiency can dramatically diminish a person's quality of life. Insufficient sleep also increases risks of health problems, such as cardiovascular disease, depression, and obesity.[5-9]

Insomnia is associated with such symptoms as not feeling well-rested after waking, daytime fatigue, irritability, depression or anxiety, excessive uneasiness about sleep, difficulty performing school or work tasks, and increased risk of accidents, especially involving an automobile.[10]

Despite the major toll insomnia takes, conventional treatment options remain far from ideal. For instance, popular *hypnotics* (also known as sedatives or "sleeping pills"), such as zolpidem (Ambien), eszopiclone (Lunesta), and temazepam (Restoril), have been consistently associated with significantly increased risk of serious adverse events, including death.[11-13] This highlights the need for safe and effective strategies to improve sleep quality, especially as up to 10% of U.S. adults use hypnotics.[13]

In this protocol, you will learn about the causes of sleep problems and simple lifestyle changes that can improve your sleep.[14,15] You will also discover emerging therapies that have achieved prolonged improvements in insomnia with potentially fewer side effects than some popular sleep drugs.[16] In addition, you will read about several *natural compounds* that modulate sleep biology and may be safer than pharmaceutical treatment options.

## 3 Defining Insomnia

Insomnia disorders are defined as persistent difficulty falling or staying asleep, waking earlier than desired, inability or resistance to going to bed at an appropriate time, or requiring an intervention to fall asleep. They are further characterized by at least one daytime impairment, such as[1]:

- Physical and/or mental fatigue
- Sleepiness
- Cognitive problems
- Social, family, school, or workplace dysfunction
- Behavioral problems
- Low energy or motivation

- Tendency to make more errors or experience accidents
- Concern about or dissatisfaction with sleep

A person who has experienced such sleep problems and daytime impairments at least three times per week for at least three months can be diagnosed with chronic insomnia, whereas less persistent insomnia is considered short-term. Finally, if these problems can be attributable to other circumstances or causes, such as noise, discomfort, medical or psychiatric issues, medications, or substance use, they fall under the category of "other insomnia disorders."[1,2]

## 4 Diagnosing Insomnia

To diagnose insomnia, a healthcare professional will take a detailed history to determine whether the patient's symptoms match the criteria for insomnia disorder (described above). A sleep questionnaire or sleep diary may be useful if the diagnosis is uncertain.[17]

Insomnia disorder is a diagnosis based exclusively on subjective information.[17] Physical exam and lab tests can be used to determine whether an underlying medical issue is likely to be a contributing factor. It is important to note that insomnia frequently co-occurs with other health conditions, including other sleep disorders, and should be considered an independent disorder unless it can be fully attributed to another cause.[1] Actigraphy, which involves the use of an unobtrusive worn device to measure limb movements over time, may be useful for providing information about sleep phase, duration, pattern, and efficiency (the amount of time in bed spent sleeping). Polysomnography, sometimes referred to as a sleep study, is performed in a sleep lab and measures brain waves, breathing, heart rate and rhythm, muscle activity, and eye movements during sleep. Polysomnography is only recommended if other sleep disorders, such as sleep apnea or parasomnias (eg, sleepwalking or nightmares), are suspected.[17,18]

## 5 Risk Factors

The following factors have been associated with increased insomnia risk[19]:

- Older age
- Female gender
- Family history of insomnia
- Other mental health, physical health, or sleep condition(s)
- Stress
- Physical inactivity
- Use of certain medications, such as stimulants
- An irregular sleep schedule
- Using electronic devices close to bedtime

Importantly, research is increasingly showing that links between insomnia and other health and sleep problems are frequently bi-directional; in other words, either condition may contribute to the other.[2]

### Gender and Hormones

Women are more likely to struggle with insomnia than men, and changes in levels of female hormones (estrogen and progesterone) that occur with menstrual cycling, pregnancy, and the menopausal transition are thought to play a role.[20,21] Almost 60% of postmenopausal women suffer from insomnia, and therapies targeting menopausal symptoms, including hormone therapies, can improve sleep.[22,23]

Sleep disorders have been linked to lower testosterone levels in both men and women. In a cohort study of more than 1,300 men age 65 and older, subjects with lower testosterone levels had lower sleep efficiency (the percentage of time spent asleep while in bed) and increased night waking, although this association was largely explained by a higher rate of overweight and obesity among those with lower testosterone.[24,25] Low testosterone levels may also worsen sleep quality, which may improve with moderate levels of testosterone replacement therapy.[26]

Lower serum testosterone levels are correlated with increased obstructive sleep apnea severity.[27,28] Obstructive sleep apnea is most common in middle-aged men, especially those who are overweight. People with obstructive sleep apnea have increased night waking, fragmented sleep, reduced sleep efficiency, and less rapid eye movement (REM) sleep, which in turn may lower testosterone levels.[25] More research is required to understand causal relationships between sleep quality and testosterone levels, especially in older or obese individuals and those with chronic health conditions.

### Obstructive Sleep Apnea—A Hidden Epidemic with Deadly Consequences

Obstructive sleep apnea is a common yet often overlooked sleep disorder that causes breathing to stop and start during sleep. It occurs when the throat muscles relax and block the airway, reducing oxygen flow. The resulting low oxygen levels in the bloodstream arouse the individual, resulting in disrupted sleep (even if they do not fully remember awakening). This pattern may be repeated five to 30 times an hour throughout the night.[29] More than 18 million Americans have obstructive sleep apnea, causing poor sleep quality, snoring, mood changes, and intractable fatigue.[30-32]

Obstructive sleep apnea is bi-directionally related to gut microbiome imbalance and increases the risks of cardiovascular and metabolic diseases.[33] It has been associated with a 68% increase in coronary heart disease in men[34] and has been linked to increased cholesterol levels, hypertension,[32,35] type 2 diabetes,[36] cancer mortality,[37] stroke, and death.[29,38]

For more information, refer to Life Extension's **Sleep Apnea** protocol.

## Psychological Health

Insomnia can be a symptom of and contributor to many mental health problems, including anxiety, depression, schizophrenia, attention deficit hyperactivity disorder, and bipolar disorder.[39-41]

Patients with untreated insomnia are two to 10 times more likely to experience new or recurrent episodes of depression. A longitudinal study of people age 65 and older in Japan found a statistically significant bi-directional relationship between insomnia and the development of depression.[42] Studies indicate insomnia is also bi-directionally related to anxiety disorders and substance use disorders.[43,44] In one longitudinal study in adolescents, insomnia symptoms were associated with the use of alcohol, cannabis, illegal drugs, and suicidal ideation and attempts.[45] Insomnia is also linked to certain personality traits, such as social introversion and the repression of feelings.[46]

One randomized controlled study in 30 healthy subjects age 21–30 found emotional reactivity to unpleasant images increased after one night of total sleep deprivation compared with a night of normal sleep in a sleep lab, which suggests that sleep may be important for emotional regulation.[47] In another controlled study, 22 people with chronic insomnia disorder and 38 healthy sleepers underwent an MRI scan during an emotional regulation task in which they were shown emotionally positive, negative, or neutral imagery, some of which was related to insomnia. Those with insomnia showed higher levels of activity in the amygdala (the emotional processing area of the brain) when shown images related to insomnia. Furthermore, during a second viewing of the images, healthy sleepers displayed habituation (dulled amygdala responses) but those with insomnia reacted inconsistently.[48]

*Psychophysiological insomnia* is a common type of chronic insomnia that can be very difficult to treat. It appears to be linked to increased activity in the "thinking" area of the brain, experienced as arousal, when going to bed. Psychophysiological insomnia is associated with excessive worrying at bedtime, specifically focused on not being able to sleep.[49] Afflicted individuals have a hard time relaxing when they go to sleep, resulting in racing thoughts. They often focus on their difficulty falling asleep, which results in more anxiety that further disturbs sleep.

Over time, poor sleep and worries about sleeping can become associated with going to bed, resulting in a pattern of chronically poor sleep that affects daytime activities. Some believe that, in addition to heightened arousal, individuals with psychophysiological insomnia may have some dysfunctional neurological inhibitory mechanisms that would normally help the mind "disengage" from daytime thought patterns.[50]

Treatment of psychophysiological insomnia includes good sleep hygiene practices, no daytime napping, limiting

caffeine intake, cognitive behavioral therapy, and approaches that acknowledge worries (such as journaling or making a worry list). A recent longitudinal case series study with 60 subjects found that co-occurring psychiatric disorders were strongly linked to negative treatment outcomes for people with psychophysiological insomnia, and people with strong social support and cognitive coping skills were most successful in treatment.[51]

### Medical Conditions

Certain medical conditions can disrupt sleep, increasing the risk of insomnia. These include chronic pain conditions, asthma and other respiratory diseases, cardiovascular disease, gastrointestinal issues, urinary tract disorders, thyroid disease, and cancer.[2,52-54]

**Nocturia** is defined as the need to urinate one or more times during the night.[55] It not only reduces sleep quality, but also increases the risks of falling and mortality, particularly in the elderly.[55,56] Nocturia can be a symptom of a medical condition, such as chronic kidney disease, diabetes, high blood pressure, congestive heart failure, chronic obstructive pulmonary disease, metabolic syndrome, or lower urinary tract problems such as prostate enlargement or overactive bladder.[55,57] In some cases, nocturia is due to polyuria (excessive urine production) at night.[57] Estrogen depletion after menopause is associated with increased risk of insomnia and nocturia in women, and treatment with hormone therapy can improve both conditions.[58] Some evidence indicates nocturia can also be caused by circadian dysregulation, suggesting a circular relationship between nocturia and insomnia.[59,60] A 2025 systematic review and meta-analysis of seven studies involving 5,396 older adults found nocturia was almost twice as prevalent in those with insomnia than in healthy sleepers, and insomnia treatment appeared to reduce nocturia.[61]

Insomnia can also be a symptom of another underlying sleep disorder, such as sleep apnea or **restless leg syndrome**. Restless leg syndrome is a condition in which a person feels discomfort in the legs and a strong urge to move them. These urges can be strongest when trying to fall and stay asleep.[62]

### Age

Insomnia symptoms have been reported to occur in 30–48% of older adults, and up to 20% have an insomnia disorder. Age-related changes in circadian rhythms and sleep architecture, particularly reduced REM and deep sleep, contribute to diminished sleep efficiency and decreased total sleep time from an average of 6.5–8.5 hours during young adulthood to 5–7 hours in those over 60 years of age.[63]

Losing sleep may also be a contributor to aging. An analysis of data from the Women's Health Initiative determined insomnia symptoms were associated with increased biological age, as measured by changes in DNA methylation in blood cells. Insomnia symptoms were also correlated with detrimental changes in immune cell balance.[64]

### Medications and Stimulants

Many prescription medications can disrupt normal sleep patterns and contribute to insomnia and sleepiness, and research shows their use is increasing.[65,66] Medication-induced insomnia can be caused by a wide variety of drugs, including decongestants, diuretics, antihistamines, monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), corticosteroids, chemotherapeutic agents, calcium channel blockers, beta-agonists, and theophylline.67-70 Some over-the-counter medications, such as energy-boosting and weight-loss products, may contain stimulants that contribute to insomnia.[71] If you think a medication may be disrupting your sleep, speak with your healthcare provider.

### Caffeine

Caffeine is one of the most widely consumed stimulants in the world. Found most commonly in coffee, tea, and some soft drinks, caffeine is used to combat sleepiness and enhance performance. Stimulants make it harder for the brain to achieve the state of relaxation needed for sleep.

The half-life (ie, amount of time it takes the body to break down 50% of a dose) of caffeine is between three and seven hours. Larger amounts and/or repeated doses of caffeine slow caffeine clearance, causing the effects to last even longer.[72] As a result, caffeine consumption can impair sleep for many hours. In a national survey that evaluated caffeine consumption and difficulty falling and staying asleep, amount of non-restorative sleep, daytime sleepiness, and typical duration of sleep attained per night, caffeine consumption was associated with insomnia

symptoms, especially daytime sleepiness.[73]

Another review of randomized controlled trials and epidemiological studies found caffeine prolonged sleep latency (ie, the amount of time it takes to fall asleep), reduced total sleep time and sleep efficiency, and worsened perceived sleep quality.[74] Older adults may be more sensitive to the effects of caffeine. Most research suggests mild caffeine consumption in the morning does not impair sleep.[75]

### Nicotine and Smoking

The use of tobacco or nicotine replacement therapy, as well as nicotine (eg, smoking) withdrawal, can contribute to insomnia.[76] One study analyzed 29 years of data from the Children and Adults in the Community Study to assess the prevalence of insomnia among heavy/continuous smokers, late-start smokers, occasional smokers, quitters/decreasers, and non-smokers. The study found chronic smokers were more likely to develop insomnia symptoms later in life.[77] Another review of data from more than 83,000 people in the Behavioral Risk Factor Surveillance System indicated current smokers or smokeless tobacco users were twice as likely to have insufficient sleep as non-smokers and non-smokeless tobacco users, independent of age, sex, race, alcohol use, and body mass index (BMI). Secondhand smoke exposure was also associated with insufficient sleep among people who never smoked or who quit.[78]

### Alcohol

While most people think of alcohol as a sedative, it increases dopamine release within the brain, which has a stimulating effect.[79] Chronic alcohol use is associated with insomnia, as is alcohol withdrawal.[80] A review of more than 60 studies indicated two to three drinks before bed may promote sleep, but this effect diminishes after three continuous days.[81] Sleep disturbances are common among those who abuse alcohol and are often associated with relapse.[82] A study examining the prevalence of insomnia in 302 alcohol-dependent patients in a treatment program in Poland found more than 60% had symptoms of insomnia, with delayed sleep being the most common symptom. A history of childhood abuse, poor health, and severity of alcoholism were predictors of insomnia in this group.[83]

A longitudinal outcomes study including 267 subjects with alcohol-dependence issues found that, at baseline, 47% of subjects were classified as having insomnia. Abstaining from or reducing alcohol intake reduced reported sleep disturbances, although insomnia persisted in 60% of cases, particularly in those with severe insomnia. Alcohol treatment programs should include insomnia evaluation during the treatment period to help focus care and prevent relapse.[84]

More information is available in Life Extension's **Alcohol: Reducing the Risks** protocol.

### Stress

People under stress often struggle with insomnia.[85] Worries about finances, work, school, and family issues may cause a state of hyperarousal, making it difficult to relax into a restful sleep state. One observational study found those who were prone to cognitive and emotional hyperarousal were more likely to experience stress-related insomnia.[86] Stress can also decrease sleep quality.[87] Major life events, such as job loss, moving, the birth of a child, death of a loved one, or divorce, may also trigger a bout of insomnia.

### Working Unusual Shifts

Not all U.S. employees have a traditional 9 a.m. to 5 p.m. job. Nearly 10% of those with a non-standard work schedule (such as rotating shifts, on-call work, or permanent night shifts) have shift-work disorder, which is a disconnect between the body's circadian rhythm and the earth's natural day-night cycle.[88] An additional 30% of shift workers experience such symptoms as excessive sleepiness when they need to be awake and alert, insomnia, problems focusing, lack of energy, and depression. Even shift workers who get enough sleep during the day may experience some of these symptoms, as their internal clock sends signals to indicate it is time to sleep during nighttime hours.[89] Shift work may also be associated with increased risk of certain diseases, including cancer and heart disease.

## 6 Complications of Insomnia

Sleep is important for overall health and well-being, and chronic insomnia can have serious mental and physical

health consequences. People with insomnia not only report a lower quality of life, but may also struggle with poor job and school performance, a higher rate of automobile accidents, and greater risks of several diseases, including heart disease, some cancers, and immunological conditions.[90]

A prospective study that followed nearly 5,000 people for 11 years concluded insomnia was associated with a greater risk of cardiovascular disease.[91] Another prospective study that followed nearly 55,000 people for 13 years found people with multiple insomnia-related symptoms had a higher risk of heart failure.[92] A study of nearly 4,000 subjects found those with a very short sleep duration (ie, less than six hours of sleep per night) were more likely to have subclinical atherosclerosis than those who slept six to seven, seven to eight, or more than eight hours per night. In addition, those with more fragmented or interrupted sleep had more areas of atherosclerotic plaque.[93]

Sleep is also influenced by, and has an influence on, the immune system. A lack of sleep can impair immunity, leaving individuals more susceptible to viral, bacterial, and parasitic infections.[94] Research indicates sleep deficiency is associated with decreased immune function and increased levels of inflammatory markers, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha), which promote inflammation.[95]

Steroid hormones and sleep are also bi-directionally connected: Hormones can influence sleep and insomnia can affect the endocrine system.[94,96] Insomnia has been associated with elevated levels of cortisol, epinephrine, and other stress hormones.[97-99] Furthermore, sleep deprivation may contribute to the development of metabolic disorders, including poor blood glucose control and obesity.[96,100,101]

Insomnia has been associated with chronic pain and musculoskeletal issues. A controlled study of 34 people, half with insomnia and half without, found those with insomnia experienced pain twice as often as those without. The insomnia group had more frequent and intense pain, more sensitivity to heat and pressure, and a dysfunctional pain inhibition system.[102] Researchers concluded that sleep quality is associated with the regulation of pain processing and ability to modulate pain. In a crossover study involving 14 healthy subjects who underwent a night of total sleep deprivation and a night of habitual sleep, researchers found that a night of sleep deprivation resulted in increased levels of sleepiness, anxiety, and sensitivity to heat and pressure.[103]

Researchers continue to investigate the potential relationship between inadequate sleep and risk of dementia. In a large observational study, researchers retrospectively evaluated people over 20 years of age with no preexisting dementia who were part of a national health insurance research database in Taiwan. The study gathered data on dementia incidence from 92,079 people with non–apnea-related sleep disorders and compared them with 92,079 healthy controls. During the time between January 2000 and December 2011, the incidence of dementia was 4.19 per 1,000 person-years in the group with sleep disorders and 2.95 per 1,000 person-years in the healthy group.[104] In another study, 6,284 Americans who were aged 65 years and older and dementia free at baseline were followed from 2011 until 2020. After adjusting for demographic and health factors, having difficulties falling asleep did not affect dementia risk, but using sleep medications was associated with an 8% increase in dementia risk.[105] Surprisingly, this study also found those whose insomnia involved trouble falling back to sleep after waking early in the morning had a 40% *lower* risk of dementia, even after fully adjusting for other factors. One proposed explanation was that these individuals may have spent more time doing social or physical activities, which helped maintain or replenish cognitive reserve. These results suggest greater complexity to the potential relationship between insomnia and dementia risk.

## 7 Treating Insomnia: Non-pharmacological Therapies

Non-pharmacological interventions have been shown to improve sleep quality in patients with insomnia. These treatment options include cognitive behavioral therapy, sleep restriction, sleep hygiene, and relaxation therapy.[106]

### Improving Sleep Hygiene and General Lifestyle Considerations

Sleep hygiene is a behavioral approach to promoting sleep. It involves such habits as having a regular bedtime routine and a consistent sleep-wake schedule, getting regular exercise, maintaining a relaxation or meditation practice, and limiting eating, drinking, and light exposure before bed.[107] One meta-analysis of 15 clinical trials found sleep hygiene improved sleep in patients with insomnia, though it was less effective than cognitive behavioral therapy.[108]

A prospective cross-sectional analysis of 548 college students examined the relationship between sleep hygiene and insomnia severity. Students reported inconsistent sleep-wake cycles and frequent worrying in bed. Improper sleep scheduling, uncomfortable sleep environments, and engaging in behaviors that create hyperarousal before bed were associated with insomnia severity. After controlling for other risk factors, sleep scheduling was most strongly associated with insomnia severity.[109] Another analysis of 130 patients admitted to a hospital burn unit found that a nurse-driven sleep hygiene protocol was successful in helping patients fall asleep more quickly and experience fewer sleep disruptions.[110]

Consider the following sleep hygiene and general lifestyle measures[90,111,112]:

- Keep your bedroom cool, dark, and quiet.
- Keep sleep and wake times consistent throughout the week.
- Avoid eating large meals two to three hours before bed.
- Limit stimulant intake (eg, caffeine, nicotine, and alcohol) during the day, especially close to bedtime.
- Limit daytime sleep.
- Spend time outdoors in natural light each day.
- Engage in daily physical activity but avoid vigorous exercise during the two hours prior to sleep.
- Create bedtime rituals (eg, taking a warm bath and listening to soft music) to improve relaxation.
- Reduce stress. People with insomnia should also review the **Stress Management** protocol.
- Use the bedroom for sexual activity and sleep only and avoid other activities, such as watching TV or reading, in the bedroom.
- If worrying about the time keeps you awake, cover the alarm clock.

### Sleep Restriction to Reset Circadian Rhythms

Sleep restriction therapy limits time in bed (including naps) to increase the biological need for sleep at night. This process usually begins by restricting time in bed to the estimated amount of time one should spend sleeping. For example, a person who stays in bed for nine hours but only sleeps six will initially restrict time in bed to six hours. This causes mild sleep deprivation in the beginning, but the sleepiness it creates trains the body to fall asleep more quickly. As the body adjusts, people can extend time spent in bed by 15 to 20 minutes until they are able to get a full night of sleep without spending extra time in bed.[113]

A study comparing sleep hygiene therapy plus sleep restriction to sleep hygiene therapy alone found sleep restriction improved sleep efficiency.[113,114] A review of evidence for sleep restriction as a stand-alone treatment for insomnia found it improved sleep efficiency and total sleep time, and researchers concluded it was an effective means of treating chronic insomnia.[115]

### Cognitive Behavioral Therapy

In 2016, the American College of Physicians recommended that cognitive behavioral therapy be the initial treatment protocol for patients with chronic insomnia.[116] Cognitive behavioral therapy helps people develop behaviors more conducive to sleep by teaching the subject to change their beliefs about sleep, develop good sleep habits, and improve their sleep environment. Traditionally, it involves regular visits to a clinician who will assess sleep patterns and work to change how the patient gets to sleep. However, self-help cognitive behavioral therapy programs have become increasingly available and may be similarly effective.[117]

Cognitive behavioral therapy for insomnia typically includes other modalities, such as sleep restriction, sleep hygiene, and relaxation training.[117,118] It may also incorporate biofeedback training or stimulus control. Biofeedback training uses a device to monitor and provide feedback about particular biological functions, such as respiration, heart rate, and/or muscle contractions, to help a person make subtle changes (such as consciously slowing breathing rate or relaxing muscles) to modulate nervous system activity. Biofeedback may help individuals better manage such conditions as anxiety, pain, and insomnia. Stimulus control focuses on removing factors associated with sleep resistance, such as an inconsistent bedtime or using the bedroom for activities other than sleep.[118]

Cognitive behavioral therapy has been shown to be an effective treatment for insomnia disorders.[119-122] A randomized controlled trial that followed 36 people for six months suggests cognitive behavioral therapy improved insomnia severity scores, sleep measures, and dysfunctional sleep beliefs.[123] A systematic review

concluded cognitive behavioral therapy may be more effective than benzodiazepine and non-benzodiazepine drugs for long-term treatment of insomnia.[124] Other research suggests cognitive behavioral therapy decreases depression, improves mental health, and is more effective in treating insomnia than hypnotic sleep aids.[12,125]

### Relaxation Therapy

Some patients with insomnia have high levels of cognitive and physiological arousal, as evidenced by increased cerebral metabolism of glucose. Relaxation therapies (including meditation, visualization techniques, breathing exercises, and progressive muscle relaxation) aim to achieve a more relaxed state prior to bedtime. Most of these techniques can be self-administered after some initial guidance from a medical professional.[106]

Social support, stress reduction techniques (including meditation and yoga), and improving coping skills for dealing with stress may be useful ways to combat insomnia in some people.[126] Research involving 30 adults with insomnia found that mindfulness-based stress reduction, including meditation training, resulted in significant improvements in sleep quality, time needed to fall sleep, and total sleep time.[127] Another study of 44 postmenopausal women age 50–65 who were not undergoing hormone replacement therapy found practicing yoga for four months lowered insomnia and stress severity scores and improved quality of life.[128]

## 8 Treating Insomnia: Pharmacologic Treatment

There are many pharmacological treatment options for insomnia, including over-the-counter medications, benzodiazepines, non-benzodiazepines, and antidepressants.[63] These medications are generally intended for occasional, intermittent use.

### Over-the-Counter Medications

Over-the-counter (OTC) medications are frequently recommended for occasional use to promote a good night's sleep. Antihistamines that block H1 receptors (also known as first-generation antihistamines), such as doxylamine (Unisom) and diphenhydramine (Benadryl), are among the most widely used OTC sleep medications, although there is little research to support their use for this purpose.[129] Blocking H1 receptors reduces congestion, sneezing, coughing, and allergy symptoms. It also causes sedation through effects on the central nervous system. Their ability to cause drowsiness and sedation has led to their use as sleep aids.[130]

There are few rigorously designed trials to definitively determine the efficacy and safety of OTC sleep aids.[131] In addition to common side effects, such as dry mouth and constipation, diphenhydramine can cause drowsiness the day after use.[132] Importantly, some people may develop a tolerance or dependence to these medications, and they may cause dangerous side effects when used with other medications. In addition, if taken for a long time and then stopped, they may worsen sleep problems.[129]

Antihistamines should be used with caution, especially in older individuals, due to increased risk of falling and confusion and a propensity to interact with other drugs.[132] One review found 50–65% of older adults misused OTC sleep medications. Drug-drug interactions and drug-age interactions were most common.[133] In 2015, the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults recommended individuals over age 65 not use products containing the ingredients diphenhydramine and doxylamine.[134]

Speak with a physician prior to using a sleep aid to ensure it does not interact with any medications you currently take or affect conditions you have. In addition[135]:

- Avoid alcohol, which causes additional sedation.
- Do not engage in activities that require being alert after taking the medication, such as driving a vehicle.
- If you find you need sleep medication for longer than two weeks, contact your healthcare provider.

### Benzodiazepines

Benzodiazepines (eg, alprazolam [Xanax], clonazepam [Klonopin], and diazepam [Valium]) were the cornerstone for treatment of insomnia until the 1990s. These medications enhance effects of the neurotransmitter gamma-aminobutyric acid (GABA)—one of the main inhibitory neurotransmitters in the brain—by binding to multiple brain receptor sites.[136] Studies have found benzodiazepines enhance sleep onset, reduce the number of nighttime waking, and improve total sleep time and sleep quality with short-term use.[63] They are generally recommended for

short-term (up to four weeks) use, but longer use may be appropriate in some circumstances.[1]

Benzodiazepines can be classified based on their duration of action. Short-acting benzodiazepines are more likely to cause withdrawal symptoms, whereas long-acting ones are more likely to leave users feeling groggy.[136] A longitudinal cohort study of more than 200 nursing home residents in Belgium found long-term use of benzodiazepines actually decreased sleep quality over the course of one year, compared to people who did not use these medications. This suggests chronic use of these drugs does not maintain a high sleep quality.[137]

### Non-benzodiazepines

Non-benzodiazepines, also called benzodiazepine-like drugs, such as zaleplon (Sonata), zolpidem, zopiclone (Imovane), and eszopiclone, act on fewer brain receptors than benzodiazepines and therefore have different side effects than benzodiazepines. As with benzodiazepines, their recommended use is limited to four weeks or less, although long-term use is common.[1] Zaleplon, one of the first non-benzodiazepines developed for the treatment of insomnia, has been proven effective in reducing the amount of time it takes to fall asleep. Its short half-life (1 hour) also reduces the risk of lasting effects the following morning, which may make it less useful for people who wake up during the night. Older adults should not take zaleplon because it is not as safe or effective as other medications available.[63]

Note while using zaleplon, some individuals experienced sleep disturbances, such as getting out of bed and engaging in such activities as driving cars, having sex, or consuming food, while partially asleep. These people were typically unable to remember what had happened the next day. Also, a person's mental health may change unexpectedly while using this medication, including increases in aggressiveness, hallucinations, memory problems, depression, confusion, and suicidal ideation. Zaleplon should only be taken under the direction and observation of a healthcare professional.

Zolpidem's half-life (about 2.5 hours) may make it more effective at reducing the amount of time it takes to fall asleep and aid in staying asleep while causing less residual daytime sleepiness.[63] A literature review found 10 mg of zolpidem in adults and 5 mg in those age 65 years and older reduced sleep latency and increased sleep duration in people with insomnia. Residual daytime effects are not common, as long as the individual is in bed for at least eight hours before waking for the day.[138] Zolpidem clears more slowly in women than men. Morning blood levels may be higher, which may affect psychomotor performance. In 2013, the Food and Drug Administration (FDA) required manufacturers to lower the recommended dose from 10 mg to 5 mg for immediate-release preparations and from 12.5 mg to 6.5 mg for extended-release forms.[63]

Eszopiclone has also been shown to be effective at improving sleep.[139,140] This medication lengthens total sleep time and helps people fall asleep more quickly. It takes longer to work than other non-benzodiazepines but also lasts longer. In 2014, 10 years after eszopiclone's approval, the FDA lowered the recommended starting dose to 1 mg due to risk of next-day impairment to driving, memory, and concentration. A double-blind study involving 91 people between ages 25 and 40 demonstrated that 3 mg eszopiclone was associated with psychomotor and memory impairment from 7.5 to 11 hours after dosing. Doses may be increased to 2–3 mg under physician guidance, but 3 mg is associated with a state of altered mental awareness.[141]

### Concerning Side Effects of Older Sleep Medications

research suggests hypnotic sleep aids (also known as hypnotics) may be associated with severe adverse events, including dependency and withdrawal, driving impairment, cognitive difficulties, and an increased risk of accidents or falls. There is also an association between use of hypnotics and increased depression, infection, and mortality rates. These risks are most commonly observed in elderly individuals and those using hypnotics over a long period of time.[1,142] Moreover, in 2012, a well-controlled study revealed an association between sleep aids, such as zolpidem, eszopiclone, and temazepam, and *a more than three-fold increase in risk of death*.[13] However, because these findings come from correlational studies, they do not prove cause. Poor sleep, which drives the use of sleep aids, may also be a contributor to or cause of the sharply increased risk of death.

A 2018 review reported 43 of 46 epidemiological studies found the use of hypnotics was associated with an increased mortality rate, and 45 of the studies found hypnotics use did not benefit patient survival.[12] Results

from two large cohort studies indicated benzodiazepine use was associated with an increase in all-cause mortality. Some researchers suggest the risks associated with hypnotics outweigh any minimal benefit. In fact, in April 2019, the FDA announced that the agency was requiring boxed warnings on eszopiclone, zaleplon, and zolpidem (eg, Ambien). A boxed warning is the most prominent warning the agency requires. This move was based on safety monitoring studies that found these drugs are associated with increased risks of engaging in potentially dangerous behaviors, such as driving, while not fully awake.[143] These medications should be used under the direction and supervision of a physician only.

### Antidepressants

As many people with depression also struggle with insomnia, antidepressant medications may help relieve symptoms of both conditions. In addition to relieving depression, some antidepressants have a sedating effect and most have no addictive properties.[132] Furthermore, most sedating antidepressants do not appear to harm sleep architecture.[144] Therefore, antidepressants are sometimes prescribed as a treatment for insomnia, even in patients without depression. Notably, the use of antidepressants is often on an off-label basis; that is, at the discretion of the treating physician even if the drug is not specifically approved to treat insomnia.[1,132]

Doxepin (Silenor) is an H1 histamine receptor antagonist with tricyclic antidepressant properties. It is sometimes prescribed to treat insomnia because of its sedative properties.[63] Doxepin has been found to increase sleep time without causing significant adverse effects and is the only antidepressant that is FDA approved for treating insomnia.[132,145,146] Research has indicated low doses (<10 mg) of doxepin can improve sleep onset, sleep maintenance, early morning waking, and sleep duration and quality over a 12-week period.[132,146,147]

Trazodone is a serotonin modulator used to treat major depressive disorders and has a mild sedative effect. Some research shows it may temporarily help people fall asleep and may be effective for short-term management of insomnia.[148,149] Trazodone can cause side effects, such as dizziness, postural low blood pressure, heart arrhythmias, and daytime sleepiness.[132] In a double-blind, placebo-controlled, crossover trial, 16 insomniacs were given 50 mg trazodone nightly for one week and placebo nightly for one week, in random order. Trazodone reduced nighttime waking and improved sleep quality, but also resulted in small but significant impairments in short-term memory, verbal learning, and arm muscle endurance.[150] Researchers concluded its risks may outweigh its benefits, particularly in elderly individuals.[63,150] In a randomized, double-blind, placebo-controlled trial involving 30 Alzheimer disease patients, individuals who took 50 mg trazodone once daily for two weeks slept 42.5 minutes more per night and had no increase in daytime sleepiness or cognitive impairment compared with placebo.[151]

Amitriptyline, a sedating antidepressant that alters brain chemistry to stabilize mood, is sometimes used to treat insomnia. Importantly, amitriptyline has been shown to increase suicidal thoughts in individuals under age 24 years. There are no controlled trials evaluating amitriptyline for insomnia in the absence of other medical conditions.[149]

Other drugs that are sometimes used to treat insomnia include mirtazapine (Remeron), a tetracyclic antidepressant, and quetiapine (Seroquel), an atypical antipsychotic drug. Limited clinical research has indicated mirtazapine may improve sleep parameters. Until more is known, it is not recommended for insomnia patients without depression.[132] In patients with psychotic disorders, quetiapine is associated with a range of serious long-term side effects, including metabolic disturbance, muscle movement disorders, and heart rhythm irregularity. Although lower doses are typically used to treat insomnia, quetiapine's safety as a sedative is still uncertain, and there is little clinical evidence for its efficacy at improving sleep.[152,153]

A 2017 review of published literature on antidepressants and sleep found low dosages of these drugs administered early at night (prior to bedtime) as part of an intervention that also involves behavioral treatments, such as cognitive behavior therapy, lead to best results.[144]

### Dual Orexin Receptor Antagonists

Orexins are neuropeptides produced by neurons in the brain's hypothalamus. Newly discovered in 1998, orexins have now been shown to play an important role in promoting arousal and wakefulness through interactions with two types of receptors, known as orexin receptor 1 and orexin receptor 2.[154] Orexins are also involved in brain

pathways related to appetite, reward, fear, and cognition.155 Orexin deficiency causes a type of narcolepsy. Narcolepsy is a condition characterized by excessive daytime sleepiness, sudden loss of muscle tone triggered by strong emotions, sleep paralysis, brief hallucinations while falling asleep or waking, and disrupted nighttime sleep. Excess or dysregulated activation of the orexin/orexin receptor system has been linked to sleep fragmentation and insomnia, as well as acute stress and stress-related disorders.[154,156]

Dual orexin receptor antagonists (DORAs) are an emerging class of drugs that improve sleep by inhibiting orexin receptors 1 and 2. DORAs appear to affect sleep architecture by increasing REM sleep while causing no change, or a decrease, in non-REM sleep.[157] DORAs have been shown to improve sleep in patients with insomnia, and researchers are currently exploring their possible role in treating neurological and psychiatric conditions associated with insomnia, such as Alzheimer disease, Parkinson disease, depression, and bipolar disorder.[158-160]

In 2014, suvorexant (Belsomra) became the first drug in this class to receive FDA approval for the treatment of insomnia resulting from difficulty initiating or maintaining sleep.[154] This approval was based on randomized controlled trials showing suvorexant improved subjective and objective measures of time to sleep onset and total sleep time, as well as subjective sleep quality. A 2017 systematic review found that excessive sleepiness, fatigue, and abnormal dreams were the most common side effects.[154,161] The FDA has since approved two other DORAs: lemborexant (Dayvigo) in 2019 and daridorexant (Quviviq) in 2022.[154]

A meta-analysis that included findings from eight randomized controlled trials involving 5,198 adult subjects with insomnia compared the safety and efficacy of suvorexant, lemborexant, and daridorexant. All three drugs, at all doses tested, were more effective for the studied outcomes than placebo. Insomnia severity scores improved similarly with each of the three drugs. The analysis showed that all the studied medications and dosages were associated with some excessive daytime sleepiness, except for the 50 mg dose of daridorexant. Unlike benzodiazepines, DORAs did not increase the likelihood of dizziness or falls in people with insomnia.[162] Other meta-analyses have shown DORAs were associated with increased risks of excessive daytime sleepiness, fatigue, dry mouth, headache, upper respiratory symptoms, and sleep paralysis.[163-165]

### Ask the Scientist: Daniel F. Kripke, MD

**Daniel F. Kripke, MD** is Professor Emeritus of Psychiatry at University of California, San Diego. He has spent decades studying sleep and the side effects of sleep medications. Life Extension (LE) asked Dr. Kripke about insomnia and risks associated with hypnotic sleep medications.

**LE:** Hi, Dr. Kripke. Thank you for taking time out of your day to share your thoughts with us. Would you start by telling us a little bit about your background and training?

**Dr. Kripke:** I am a research psychiatrist who opened one of the country's first sleep clinics to study the causes of depression. Insomnia and depression are often linked. They have common genetic predispositions, and depression seems to cause insomnia, and vice versa.

**LE:** You have been studying the association between hypnotic sleep aids and adverse outcomes for quite a long time. Why were you drawn to this area of study?

**Dr. Kripke:** American Cancer Society data from one million questionnaire participants showed that self-reported long sleep duration and short sleep duration predicted early death.[166] Over 40 years ago, I noticed that their data showed that reported use of sleeping pills predicted early death more so than insomnia did. I have since been trying to clarify the risks of sleeping pills.

**LE:** What are some of your most compelling findings related to the risks associated with hypnotic sleeping pills?

**Dr. Kripke:** People who take hypnotics are at significantly greater risk of mortality than people who do not take them. Almost all of 46 studies from all over the world demonstrate this, but the amount of risk has varied greatly in the research due to variations in study methodology.[12] There is uncertainty surrounding how much of risk is caused by sleeping pills. Controlled clinical trials show that hypnotics can cause depression and are associated with increased risk of suicide. Also, hypnotics considerably increase the risk of infections, likely including an increased risk of potentially severe infections, such as pneumonia. Finally, hypnotics impair automobile driving and may increase the risk of falls and other accidents.

**LE:** One of the limitations with the research in this area is that much of it is correlational and not necessarily reflective of a causal link between sleeping pills and negative outcomes. Are there trials underway or planned that you think will overcome this uncertainty?

**Dr. Kripke:** The data for depression and infection include randomized studies that establish causality. Some studies of autopsied deaths, especially those linked to opioids, list hypnotics as contributing or primary causes. Hypnotics are used to put animals to sleep (permanently) and for executing prisoners, so there is no question that, at excessive doses, these drugs can kill. The question is how often they are lethal in combination with risky behavior, health problems, and other medications. There are studies planned to clarify these uncertainties, but I cannot tell you that any definitive study has already begun.

**LE:** You have expressed some frustration in some of your past published work that the FDA has not adequately responded to these concerns about hypnotics and adverse outcomes. Have you seen any evolution in the agency's position recently? If not, what is keeping the FDA from taking action?

**Dr. Kripke:** The FDA has been essentially unresponsive to the new research that demonstrates hypnotic risks. Moreover, the FDA has the authority to order manufacturers to do clinical trials of marketed drugs to establish the causality of newly recognized risks, but it has made no effort to do so. The FDA has its own animal testing facilities that could be used to help clarify the cancer risk associated with these drugs. In my opinion, the FDA position is an unscientific one.

**LE:** Do you think hypnotic sleep aids actually work? What does the evidence say?

**Dr. Kripke:** Recent studies sponsored by the government's Agency for Healthcare Research and Quality (AHRQ) and by the NIH have found that there is weak evidence to suggest that hypnotic sleep aids make people sleep 10 or 20 minutes more per night. It is generally agreed that hypnotic sleep aids do not make people objectively more alert and productive the day after taking them at bedtime. In fact, much of the evidence suggests sleeping pills make people sleepier and reduce performance time the next day. Moreover, there is absolutely no evidence that sleeping pills improve general health.

**LE:** Are there any newer sleep aids that you think are better options than hypnotics? If so, what are they and why would you prefer them over hypnotics?

**Dr. Kripke:** The AHRQ report and the American College of Physicians guidelines conclude that no drug is as useful for insomnia as cognitive behavioral therapy. I think that when circadian rhythm disturbances or depression are associated with cases of insomnia, bright light treatments are superior to hypnotics. It would be nice to have more long-term studies comparing light versus hypnotics.

**LE:** What can people who do not want to take any form of sleeping medication do to get a better night's sleep? Are there any particular habits that you suggest?

**Dr. Kripke:** First of all, there are many reasons people want to sleep better, and they need different approaches. In the sleep clinic, we commonly see patients who think there is something wrong with their sleep when it really is not since their sleep pattern is normal. Part of this comes from drug company-sponsored propaganda suggesting that everyone needs eight hours of sleep or more, which is not true in all cases. Family doctors, psychologists, and sleep specialists can advise what treatments to try first. There is useful information about cognitive behavioral therapy for the treatment of insomnia on the internet or at the library. The U. S. Department of Veterans Affairs now offers its patients a free [**app**] that provides [assistance with] cognitive behavioral therapy, and there are several commercial websites that offer similar services for less than the cost of sleeping pills.

**LE:** Do you find that people who suffer with insomnia typically make certain mistakes or engage in certain habits that contribute to their insomnia? If so, what are they, and how can they be avoided?

**Dr. Kripke:** There are many causes of insomnia. One of the most common is spending more time in bed than is needed to sleep: spending less time in bed results in less insomnia. Another common problem is getting too little bright light exposure. People feel better and sleep better with at least an hour a day of outdoor daylight or its equivalent. Since exercise is also helpful, walking for 30 minutes to an hour a day in daylight is a simple and

effective treatment. Avoiding too much caffeine and alcohol can promote healthy sleep patterns, as well as not using cell phones, tablets, and computer screens shortly before bedtime. The bright bluish light of modern display screens can be neutralized with software that decreases blue light or by wearing orange (blue-blocking) glasses for an hour or two before bedtime. An irregular sleep schedule may also contribute to insomnia. Staying up late on weekends may make it difficult to get to sleep early enough on Sunday night, which makes it hard to wake on time on Monday morning.

**LE:** Your comments have been very interesting and insightful, Dr. Kripke. Thanks again for sharing your knowledge with us.

## 9 Novel and Emerging Treatments

### Targeting Melatonin Receptors

Melatonin is a hormone involved in controlling the body's sleep-wake cycle. Melatonin activates two receptors, MT1 and MT2. These receptors are found mainly in a region of the brain that controls circadian rhythms but are also present in other parts of the body. Supplementing with melatonin modulates central nervous system activities by activating MT1 and MT2 receptors.[167] Drugs that stimulate these receptors, known as melatonin receptor agonists, mimic melatonin by binding to and activating the same receptors, inducing sleep. Although these drugs are not identical to melatonin supplements, they have been shown to help improve sleep in insomnia patients.[132]

*Ramelteon* (Rozerem) is an FDA-approved insomnia medication that binds to and activates MT1 and MT2 melatonin receptors.168 Rather than depressing the central nervous system, ramelteon promotes sleep by regulating the sleep-wake cycle.[169] It is highly selective for the melatonin receptors MT1 and MT2, which minimizes its potential to cause side effects and has a half-life of just over one hour.[141,170-172] Ramelteon has been reported to cause side effects, such as dizziness, sleepiness, fatigue, and headache. It can be used long term without causing dependence or withdrawal symptoms.[132,169]

In a study of adults age 65 and older, ramelteon significantly reduced sleep latency over five weeks with no significant side effects.[173] In another randomized, double-blind, placebo-controlled trial in adults age 18–64, subjects who received 8 or 16 mg of ramelteon had reductions in sleep latency and sleep onset.[174]

*Tasimelteon* (Hetlioz) is a high-affinity MT1-MT2 receptor agonist that regulates sleep and shifts circadian rhythms. It was originally developed to treat non–24-hour sleep-wake disorder, in which individuals cannot train the body clock to the 24-hour dark-light cycle. In one placebo-controlled clinical trial in healthy individuals, tasimelteon reduced sleep latency and increased sleep efficiency with no side effects.[175]

Animal research has demonstrated that the melatonin receptor MT2 promotes deep sleep. Drugs that specifically target the MT2 receptor are beginning to emerge, including IIK7 and UCM765. Animal research suggests these medications increase amount of deep sleep and reduce sleep latency in mice.[176,177] However, further human research is needed to confirm safety, efficacy, and potency.[178]

### 5-HT2 Receptor Antagonists

5-HT receptors, 5-HT2A and 5-HT2C, are of particular interest with regard to sleep. Activation of these receptors interferes with deep sleep.[181] Therefore, therapeutics that reduce signaling through these receptors to facilitate high-quality sleep are being developed. While both animal and human data suggest blocking 5-HT2A/C signaling appears to be a promising mechanism for improving sleep quality, more research is needed.[183,184]

Serotonin (5-hydroxytryptamine or 5-HT) is a neurotransmitter that plays a role in regulating sleep, appetite, thermoregulation, emotion, and cognition.[179] It acts by binding to and activating various 5-HT receptors in the ventrolateral preoptic nucleus (VLPO), the main structure of neurons that trigger non-REM sleep.[180,181] Impairments in 5-HT transmission have been linked to depression, anxiety, and sleep disorders. In one study, 5-HT-deficient mice demonstrated a disrupted sleep-wake cycle with an increase in restless sleep (a period of sleep with frequent wakings).[182]

In animal research, sleep-promoting neurons in the VLPO can be characterized by their response to

neurotransmitters, such as noradrenaline and 5-HT. Those inhibited by 5-HT are known as Type 1 neurons and those excited by 5-HT are known as Type 2. Type 2 neurons are involved in sleep initiation and triggering activation of Type 1 neurons. Type1 are thought to be responsible for sleep maintenance through inhibition of the brain's arousal system.[179]

### Propofol: Novel Use of an Anesthetic to Reset Sleep Rhythms

*Propofol* is a rapid, short-acting anesthetic often administered intravenously for the induction and maintenance of sedation during monitored anesthesia. While propofol is typically used for sedation during surgeries or other medical procedures, some researchers have found that low doses may help restore normal sleep rhythms.

Propofol induces a state of unconsciousness resembling non-REM sleep. Brain activity during anesthesia and sleep shares many similarities but also distinct differences.[185] Interestingly, propofol sedation without surgery has been shown to alter diurnal melatonin secretion in animals, suggesting the drug can influence the body's circadian clock system.[186]

In a randomized, placebo-controlled, double-blind clinical trial, subjects receiving a two-hour infusion of propofol for five consecutive nights showed improvement in sleep onset latency (ie, shorter time needed to fall asleep), quality of sleep, ease of waking up, and behavior after waking. These improvements persisted for six months, suggesting the benefits of propofol could continue after initial treatment. In addition, subjects showing no response to traditional agents, such as zopiclone or zolpidem, before study treatment were able to effectively use them on occasion after treatment, suggesting propofol restored the brain's response to conventional sleep aids.[16] The study showed using propofol for a short period of time at the same time each night could help reset the body's natural circadian rhythm, providing long-term benefits for people with chronic refractory insomnia.

As of mid-2025, no sleep centers that we are aware of are routinely offering propofol, which requires strict medical vigilance and adherence to safety protocols to avoid overdose. The novel use of propofol to reset sleep patterns, administered under carefully controlled clinical conditions, is an area of insomnia research that requires further study.

## 10 Nutrients

### Melatonin

Melatonin, a hormone made in the brain's pineal gland, is a major regulator of the body's sleep-wake cycle. The pineal gland's release of melatonin into the bloodstream peaks in the evening, coinciding with nighttime darkness, and falls in the morning, stimulated by the onset of daylight. Melatonin is also produced in a number of other tissues, where it helps synchronize local circadian rhythms.[187]

Low melatonin levels have been linked to insomnia, particularly in the elderly. In a clinical review, serum melatonin levels were reported to be significantly lower and the time of peak melatonin values delayed in elderly subjects with insomnia compared with age-matched healthy controls.[188] A meta-analysis of 19 randomized placebo-controlled trials including 1,683 patients found that melatonin supplementation improved sleep quality, increased total sleep time, and decreased sleep latency.[189,190] Other studies suggest it may enhance alertness after sleep[191] and reduce the number of times people wake up during the night.[192] Melatonin may also improve nocturia, a condition closely related to insomnia. A systematic review reported melatonin or melatonin receptor agonist therapy improved nocturia in eight of nine clinical trials.[193]

While melatonin has been found to improve sleep quantity and quality, questions persist about optimal timing and dose. A 2024 systematic review that examined findings from 26 randomized controlled trials yielded several important findings[194]:

- Melatonin had a stronger effect in healthy subjects than in those diagnosed with insomnia.
- Sleep latency gradually decreased and total sleep time increased as the dose of melatonin increased from 0.5 mg, with peak effects seen at **4 mg per night** (higher doses did not result in additional benefit).
- Taking melatonin earlier in the night (longer before going to bed) enhanced its effect on sleep latency and

total sleep time. The greatest benefit was seen at **3–3.5 hours prior to bedtime**, the longest interval for which there was evidence.

The enhanced effect of a three-hour lead time for melatonin supplementation may be related in part to its synchrony with normal patterns of melatonin secretion, since, in healthy adults, levels of endogenous melatonin have been observed to peak about two hours before sleep.[194-196]

These findings suggest the potential benefits of melatonin may be underestimated because of typical sub-optimal dosing (1–2 mg) and timing (30–60 minutes before bedtime) recommendations. Clinical trials are needed to determine whether optimal dosing and timing may improve melatonin's efficacy in insomnia patients. However, the aforementioned analysis does provide a rationale for individuals who have tried melatonin (taken shortly before bedtime) without success to try again with dosing about three hours before bedtime.

### Nobiletin

Circadian rhythms are biological processes that vary during the natural 24-hour day-night cycle. Maintaining consistent and healthy circadian rhythms promotes overall health and well-being, including healthy sleep patterns.[197,198]

The human body contains two regulatory elements that respond to circadian rhythms: the central clock and peripheral clocks.[199] Melatonin supplementation can help modulate the central clock. Nobiletin, a flavonoid derived from citrus peels, helps modulate peripheral clocks.[200,201]

Preclinical research suggests nobiletin may protect against metabolic syndrome and age-related health deterioration in part by helping regulate peripheral clocks. When given to obese mice, nobiletin counteracted metabolic syndrome and increased energy expenditure.[201] Another animal study demonstrated that nobiletin reduced symptoms of delirium in mice. Researchers believe the mechanism of action involves regulating the expression of the proteins that help maintain a stable circadian rhythm.[202] Nobiletin may also help alleviate circadian rhythm disorders and jet lag.[203]

### L-tryptophan

L-tryptophan is an amino acid that serves as a precursor for serotonin and melatonin.[204,205] L-tryptophan supplements may increase the amount of melatonin made by the pineal gland, leading to better sleep.[206] L-tryptophan has long been of interest in the sleep field. Research dating back more than 44 years found that 1 gram reduced the amount of time needed to fall asleep.[207] Like melatonin, L-tryptophan levels decrease with age[208]; therefore, L-tryptophan supplementation may aid in the treatment of insomnia in the elderly.

One animal study found tryptophan supplementation helped prepare the body for sleep by reducing core body temperature and enhancing rest at night. It also lowered levels of IL-6, an inflammatory cytokine.[206] In one small human clinical trial, intravenous infusion of L-tryptophan caused dramatic increases in plasma melatonin levels and had a sleep-inducing effect, regardless of whether it was administered in the daytime or nighttime.[209] In addition, L-tryptophan may help alleviate some forms of depression, which can exacerbate insomnia.[210]

An analysis of data from the National Health and Nutrition Examination Survey (NHANES) (2001–2002) involving more than 29,000 individuals determined higher tryptophan intake was associated with longer sleep duration.[211] Another study examined whether consumption of cereal grains fortified with tryptophan improved the sleep-wake cycle in 35 individuals age 55–75 years. The study compared the effects of three diets, each followed for three weeks: usual diet; a diet that included standard cereal grains, eaten at breakfast and dinner, providing 22.5 mg tryptophan per 30 grams; and a diet that included enriched grains providing 60 mg tryptophan per 30 grams. Eating tryptophan-enriched cereal grains was found to increase sleep efficiency and total sleep time and decrease sleep fragmentation and latency.[212]

Another randomized study involving 33 male college students investigated the effects of tryptophan consumption at breakfast and daytime light exposure on melatonin secretion and sleep. Subjects ingested either a tryptophan-poor meal paired with dim light, tryptophan-rich meal with dim light, tryptophan-poor meal and bright light, or tryptophan-rich meal with bright light exposure for four days. The combination of bright light and a tryptophan-rich meal at breakfast resulted in the greatest evening rise in melatonin levels.[213]

### Glycine

Glycine, a non-essential amino acid, also acts as a quieting neurotransmitter and helps support bone health, digestion, and metabolism.[214] In one randomized, single-blind, crossover trial in 11 healthy volunteers, 3 grams glycine one hour before bedtime led to shortened time to sleep onset and improved sleep satisfaction without next-day sleepiness.[215] In a randomized, double-blind, crossover trial, 3 grams glycine before bedtime improved sleep quality and next-day fatigue.[216] In a randomized, single-blind, crossover trial, 10 healthy men underwent experimental sleep restriction to 75% of usual and were given 3 grams glycine before bed for three nights and placebo for three nights, in random order. Glycine was found to improve performance on memory, cognition, and reaction-time tests and self-rated fatigue and sleepiness levels compared with placebo.[217]

### Magnesium

Magnesium is a mineral that plays a role in cellular communication, energy production, muscle function, blood sugar maintenance, and regulation of circadian rhythms.[218] The recommended dietary allowance (RDA) for magnesium is 420 mg for men and 320 mg for women age 31 and older.[219]

Magnesium is needed for healthy sleep regulation.[220] Magnesium deficiency is associated with shorter sleep duration[221] and may cause inflammation, which could result in conditions associated with poor sleep, including diabetes and cardiovascular disease.[222] In addition, research suggests intracellular magnesium concentrations decline as sleep restriction increases.[223]

One clinical trial found magnesium supplementation helped relieve insomnia related to restless legs.[224] In a double-blind placebo-controlled clinical trial, 43 patients in long-term care with chronic insomnia were given 5 mg melatonin, 225 mg magnesium, and 11.25 mg zinc or placebo one hour before bedtime every night for eight weeks. The treatment group saw improved sleep quality and improved quality-of-life measures compared with placebo.[225]

A form of magnesium known as *magnesium L-threonate* may be beneficial for sleep, as it penetrates the blood-brain barrier more efficiently than other forms of magnesium.[226,227]

### Zinc

Zinc, a trace element that is essential for many biological functions, including immune health and neurocognition, may help reduce the risk of inflammatory diseases.[228] According to a literature review, higher serum zinc levels have been linked to healthy sleep duration and quality, and supplementing with oral zinc may increase both amount and quality of sleep.[229] One randomized controlled trial found zinc, along with magnesium and melatonin, reduced insomnia.[225] An observational study in which blood and hair levels of zinc and copper were measured in 126 women found those with the highest blood and hair zinc-to-copper ratios were more likely to have optimal sleep duration than women with the lowest zinc-to-copper ratios.[230] In an animal study, mice fed a yeast extract containing zinc had increased levels of non-REM sleep and decreased motor activity levels when sleeping.[231]

How zinc supports sleep patterns remains unclear, but some researchers speculate that oral administration of zinc rapidly increases blood levels, crosses the blood-brain barrier, and activates signaling pathways involved in circadian regulation and sleep induction.[229]

### Valerian

Valerian (*Valeriana officinalis*) is a perennial flowering plant that has been used traditionally for treating sleep problems, anxiety, and stress.[232] Valerian root contains several compounds with sedative effects, including valerenic acid and valepotriates. Valerian root is believed to increase the activity of gamma aminobutyric acid, or GABA, the body's main quieting neurotransmitter.[233,234]

In one randomized, triple-blind, controlled trial involving 100 postmenopausal women struggling with insomnia, treatment with 530 mg valerian root for four weeks resulted in improved sleep quality.[235] An animal study found a mixture of hops and valerian improved sleep parameters, including total sleep time, by modulating GABA signaling.[236]

One study involving 202 patients with insomnia found 600 mg valerian per day for six weeks showed comparable efficacy to a commonly prescribed hypnotic (oxazepam).[237] A review of relevant studies indicated valerian had a favorable safety profile, no known interactions with common medications, and could be recommended as an

option for people struggling with sleep issues.[238] The typical dose of valerian is about 300–600 mg, 30 to 120 minutes before going to sleep.[239] It may take up to two weeks of daily use for the full sedative effect of valerian to manifest.[240]

Valerian may also be useful when applied topically. One randomized clinical trial involving 85 severely ill patients found that acupressure with valerian between the hours of 7:00 p.m. and 10:00 p.m. resulted in increased sleep time and less frequent night awakenings.[241]

### Chamomile

Chamomile (*Matricaria chamomilla*) is a popular herb often used as a tea to promote sleep and relaxation.[242,243] The dried flower extracts of chamomile contain terpenoids and flavonoids that may reduce inflammation and help treat insomnia, ulcers, wounds, pain, and muscle spasms. Sedative properties of this herb are believed to be due to certain flavonoids that may modulate benzodiazepine-receptor signaling in the brain.[244]

One randomized, placebo-controlled, double-blind study involving 57 people with a history of anxiety and depression found that chamomile supplementation reduced depressive symptom scores.[245] In a randomized controlled trial of 80 postnatal women, drinking chamomile tea for two weeks helped alleviate symptoms of depression and improve sleep quality.[246] In a randomized controlled trial, 200 mg chamomile twice daily for 28 days improved sleep quality in a group of elderly subjects.[247] In another clinical trial of 77 elderly subjects, 400 mg chamomile twice daily improved reported sleep quality measures.[248] One randomized placebo-controlled clinical trial found 270 mg chamomile twice daily for 28 days improved daytime functioning of 34 subjects with sleep problems.[243]

### Passionflower

Passionflower (*Passiflora incarnata*) has long been used to treat anxiety and insomnia in Europe.[249] The active compounds in passionflower appear to interact with the GABA and opioid systems.[250-252] Extracts of this plant have shown sedative, anti-diabetic, and anti-asthmatic activities in preclinical research.[249]

In one randomized double-blind trial involving 78 subjects with insomnia, an herbal combination containing hops, valerian, and passionflower was shown to improve sleep time, sleep latency, and night awakenings similarly to treatment with the hypnotic drug zolpidem after two weeks.[253] One randomized study compared supplementation with either passionflower or St John's wort in 59 women with menopausal symptoms experiencing sleep disturbances and depression. After six weeks, both groups demonstrated improved sleep quality.[254] In an animal model, passionflower was shown to reduce anxious behavior.[251] Another animal study found that passionflower-derived compounds prevented dependence on the benzodiazepine diazepam when given with the drug over a three-week period.[255] While this extract has a good safety profile, more rigorous clinical data is necessary to assess its efficacy in humans.

### Ashwagandha

Ashwagandha (*Withania somnifera*) is an Indian herb used for centuries as a wellness-promoting tonic. Ashwagandha may be beneficial for reducing anxiety, promoting calmness, and treating insomnia. This herb has been best characterized for its effects on stress. A randomized, double-blind, placebo-controlled trial in 64 individuals struggling with chronic stress found 300 mg of an ashwagandha extract twice daily for 60 days reduced reported stress and serum cortisol levels.[256]

Several animal studies have found that this extract improved the ability to handle stress and reduced anxiety.[257-259] In vitro research suggests a component of this herb, withanone, protects nerve cells from oxidative stress.[260,261] Because emotional stress can be a significant contributor to insomnia, ashwagandha may help indirectly improve sleep by improving the response to stress.

In a randomized, double-blind, placebo-controlled trial, 144 subjects with non-restorative sleep took 120 mg of a standardized ashwagandha extract or placebo once daily for six weeks. Those who took ashwagandha reported a 72% increase in sleep quality versus a 29% increase in those who took placebo. Moreover, the group taking ashwagandha had improved sleep efficiency, total sleep time, and sleep latency, as well as quality of life scores.[262]

Ashwagandha has also been found to directly improve sleep in animal models. In one animal study, sleep-

deprived rats given an ashwagandha extract showed improvements in behavioral tests, indicating the supplement may help mitigate the cognitive and memory impairments associated with insomnia. The rats also had decreased signs of cellular stress and apoptosis (programmed cell death) in the hippocampus, the brain region involved in memory, emotions, and behavior.[263-265]

### Lemon Balm

Lemon balm (*Melissa officinalis*) is an herb from the mint family traditionally used for its calming and anxiety-reducing effects.[266,267] One randomized, double-blind, placebo-controlled, crossover study with 18 healthy participants showed a single 600 mg dose of lemon balm improved mood and significantly increased self-rated calmness one hour later, following a 20-minute set of stress-inducing tasks.[268] Lemon balm has also been investigated for the treatment of sleeping problems.

Research indicates rosmarinic acid, ursolic acid, and oleanolic acid are the active compounds in lemon balm, with rosmarinic acid being responsible for most of the activity associated with this herb. Lemon balm may inhibit the breakdown of the neurotransmitter GABA.[269] In a randomized, controlled, crossover trial in 11 healthy people, taking a lemon balm extract providing 500 mg rosmarinic acid per day for seven days was found to be safe and tolerable.[270]

In an open-label prospective study, 20 individuals with indications of stress took a standardized lemon balm extract for 15 days. Improvements in anxiety and insomnia symptoms were reported.[271] In a randomized placebo-controlled trial, 100 postmenopausal women with sleep disorders received a combination of valerian and lemon balm. The treatment group experienced a reduction in sleep disorder symptoms.[235] An uncontrolled study in 918 children with restlessness and difficulty sleeping found tablets with 160 mg valerian and 80 mg lemon balm, taken at doses of up to two tablets twice daily for at least four weeks, improved symptoms in 81% of participants.[272]

### Lavender (as essential oil aromatherapy)

Aromatherapy is an alternative medicine practice that utilizes plant oils to treat health problems. Lavender oils have been extensively studied for the treatment of insomnia. A randomized controlled clinical trial involving 79 college students with sleeping difficulties found that inhaled lavender combined with good sleep hygiene practices was more effective than sleep hygiene alone in improving sleep quality.[273] In another trial, 67 middle-age women with insomnia were randomized to either inhale lavender oil for 20 minutes twice weekly for 12 weeks or participate in a control group receiving sleep hygiene education. The treatment group experienced an improved quality of sleep compared with the control group.[274]

In a four-week study involving 28 postpartum women struggling with anxiety and depression, subjects were either randomized into a group that inhaled a blend of rose otto and lavender essential oils or instructed to avoid essential oil use during the study period. The aromatherapy group had significant improvements in depression and anxiety scores, with no adverse side effects reported.[275] A single-blind randomized controlled trial in 15 healthy Japanese students found exposure to lavender oil aroma for five days reduced self-reported sleepiness on waking.[276] In an animal model, lavender oil use for seven days reduced behaviors associated with depression and anxiety. Exposure to the oil also has been shown to decrease aggressive behaviors and improve social interactions.[277]

Oral lavender may also help combat sleep problems. In a multi-center, randomized, double-blind trial, six weeks of treatment with oral lavender oil (Silexan) was found to be as effective as the benzodiazepine lorazepam for reducing anxiety and improving sleep, without causing sedative side effects, in patients with generalized anxiety disorder.[278]

Lavender is thought to possess antioxidant abilities and reduce inflammatory pathways. It also may alter ion channels in neurotransmitter junctions, which suggests it may be beneficial in Alzheimer disease patients. The oil may act via the limbic system to quiet the central nervous system when absorbed through the skin after topical application. While lavender oil appears safe and tolerable, and evidence supporting its use is promising, more clinical trials with long-term data are required to further clarify its role in promoting sleep and relaxation.[277]

### Saffron

Saffron, a spice derived from the *Crocus sativus* flower, has been widely used as a flavoring agent and traditionally used to treat depression and asthma. It has powerful antioxidant properties, and preclinical studies indicate its major active compounds safranal, crocin, and crocetin may have anti-tumor and anti-atherosclerotic properties.[279] Animal and in vitro research suggest saffron may have a role in treating Alzheimer disease, cardiac ischemia, and age-related macular degeneration.[280] Other preclinical studies indicate saffron and crocin may have neuroprotective properties.[281]

Preliminary evidence suggests saffron may promote sleep. Animal studies on safranal indicate it may support non-REM sleep and decrease sleep latency.[282] One placebo-controlled human trial examined the effect of 300 mg of saffron on sleep quality in 50 diabetic patients. After one week, sleep quality improved in the treatment group.[283] However, more high-quality human data is necessary to determine if and how saffron can be used to treat insomnia.

### Honokiol

Honokiol is a lignan (a type of fiber) extracted from the bark, seeds, and leaves of the Magnolia tree. It has traditionally been used to treat mood disorders, including anxiety and depression,[284] and is believed to have anti-tumor, anti-inflammatory, and antioxidative effects.[285] It can cross the blood-brain barrier, resulting in enhanced bioavailability, and research suggests it enhances GABA receptor activity in the brain's hippocampus and exerts neuroprotective effects in the central nervous system.[286,284]

In one animal study, mice given honokiol experienced shortened sleep latency and increased non-REM sleep.[287] Several older studies with animal models support these findings, including one in which mice given seven daily treatments of two different traditional plant-based tinctures (Hangekobokuto and Saibokuto) had reduced anxiety and improved maze tests scores. These effects appeared to be related to the honokiol content, as varying the chemical content of the samples still produced similar results as long as honokiol was contained in the sample, and honokiol-free preparations were not effective.[288] Mice administered 20 mg/kg honokiol showed reduced anxiety levels with no reduction in motor function during a maze test.[289] Another animal study demonstrated that honokiol had similar anxiolytic effects as diazepam, but appeared not to cause amnesia and dependence.[290] While these results are promising, more human clinical trials are required to understand how honokiol affects sleep.

### Danshen

Danshen (*Salvia miltiorrhiza)* is an herb traditionally used to promote sleep and enhance blood circulation, thus improving cardiovascular health.[291] The main components of *S. miltiorrhiza* include rosmarinic acid and salvianolic acid. It is often used in combination with borneol for better pharmacological results.[292] Early animal research suggests danshen has anxiety-relieving properties.[293] However, well-designed clinical data is lacking, and adequate research must be carried out to understand how danshen alters sleep.

### Bioactive Milk Peptides

Certain peptides derived from the enzymatic breakdown of milk proteins may relieve stress-related sleep disorders. These peptides are believed to act on GABA receptors in the brain, inducing relaxation and sleep. In one study, these bioactive peptides increased time spent sleeping and reduced the amount of sleep needed after just two weeks of treatment. Another randomized, double-blind, placebo-controlled study of 63 women found 150 mg daily of the milk protein alpha-s1 casein hydrolysate reduced stress-related symptoms, including sleep difficulties.[294,295]

## Nutrients Targeting Nighttime Urinary Frequency and Urgency

Frequent trips to the bathroom to urinate at night can substantially undermine sleep quality and quantity. Several nutrients have been shown to improve some aspects of urinary function and may thereby be of interest to individuals whose sleep is frequently disrupted by bathroom trips.

### Beta-sitosterol

Beta-sitosterol is a plant compound found widely in foods and medicinal herbs. It has been shown to improve urinary symptoms and flow measures in men with benign prostatic hyperplasia (BPH), a condition frequently associated with sleep disruption in older men.[296-298] Advanced computational laboratory research has suggested that beta-sitosterol may also affect signaling pathways involved in relaxation and sleep.[299]

### Lindera, Crataeva, and Eqisetum

*Lindera aggregata* (lindera), *Crataeva nurvala* (three-leaved caper), and *Equisetum arvense* (horsetail) are from Chinese, Ayurvedic, and Western herbal medicine traditions, respectively. Each has been used historically to improve bladder tone, treat frequent urination, and reduce incontinence. In a randomized placebo-controlled trial involving 150 patients with overactive bladder and/or urinary incontinence, a combination of equisetum, crataeva, and lindera, taken for eight weeks, substantially reduced nocturia and difficulty sleeping, as well as daytime frequency, urging, and incontinence.[300]

### Lycopene

Lycopene is a carotenoid found in tomatoes and other yellow, orange, and red fruits and vegetables. High lycopene intake appears to help protect against BPH and low lycopene levels have been correlated with lower urinary tract symptoms in older men.[296,301] In observational studies, lower carotenoid serum levels were associated with shorter sleep duration and lower lycopene intake was linked to greater difficulty staying asleep.[302,303]

### Pygeum

*Pygeum africanum* is one of the most-studied medicinal plants for the treatment of BPH and urinary symptoms.[296] Pygeum has been shown to be effective for improving lower urinary tract symptoms, including nocturia, in men with BPH.[304]

## Update History

### *Disclaimer and Safety Information*



## References





†Ratings based on results of the 2025 ConsumerLab.com Survey of Supplement Users. Multivitamin rating based on results of the 2024 ConsumerLab.com Survey of Supplement Users. For more information, visit **www.consumerlab.com/survey**.

**These statements have not been evaluated by the Food and Drug Administration.**
**These products are not intended to diagnose, treat, cure, or prevent any disease.**