

## Insomnia

Good, refreshing sleep is essential for health. There is no doubt that chronic insomnia is frustrating, but there is also evidence that insomnia is linked to early death and serious declines in quality of life. Studies show that poor sleepers receive fewer promotions, have increased rates of absenteeism, and tend to demonstrate poor productivity (Leigh JP 1991; Rajput V et al 1999).

Insomnia is everywhere in the industrialized world. A recently published survey indicates that insomnia afflicts slightly more than 27 percent of adults in the United States (Leger D et al 2005). In an international study of insomniacs, the most common complaint was poor “sleep maintenance,” cited by 73 percent, while difficulty falling asleep came in second, at 61 percent. About half the study participants (48 percent) cited “poor sleep quality” as their predominant symptom (Leger D et al 2005).

Not surprisingly, a majority of insomniacs studied are “somewhat” or “very” bothered by their insomnia, noting that it adversely impacted their daily quality of life (Leger D et al 2005). Insomnia often results in daytime sleepiness, reduced cognitive performance, and potentially dangerous inattentiveness. One recent study, conducted in Brazil, found that an alarming 22 percent of long-haul truckers had fallen asleep at the wheel. Astonishingly, nearly 3 percent reported falling asleep on the job daily (Canani SF et al 2005).

There is no single patient type when it comes to poor sleep, although women tend to suffer from insomnia in greater numbers than men. Insomnia may be associated with a wide variety of prescription drugs and other conditions, such as Parkinson’s disease, Alzheimer’s disease, coronary artery disease, cancer, dementia, breathing difficulties (e.g., sleep apnea), or chronic conditions such as rheumatism (Graci G 2005; Power JD et al 2005).

Hoping to better understand the connection between insomnia and diseases, researchers have conducted studies examining the levels of various chemical signals (called cytokines) in sleep and insomnia. They have discovered that nighttime secretion of the cytokine interleukin-6 is significantly increased in patients with primary insomnia (Burgos I et al 2005). Interleukin-6 is a pro-inflammatory cytokine that is linked to cardiovascular and other diseases. Researchers have found that lack of sleep correlates with interleukin-6 production both day and night, which might also explain why so many insomniacs experience daytime sleepiness: interleukin-6 is involved in regulating sleep (Vgontzas AN et al 2005). Additional studies have found that tumor necrosis factor, another pro-inflammatory cytokine, is increased in insomniacs during the daytime and that levels of these two cytokines are closely related to the level of fatigue experienced (Vgontzas AN et al 2002). These findings mean that insomnia may promote a constant state of low-grade inflammation that may accelerate many diseases of aging.

### SLEEP AND AGING

As people age, their sleep gradually becomes more disjointed, shallower, and shorter. Sleep cycles through phases throughout the night. Early stage-1 sleep is the lightest stage. Delta sleep, or stage-4 sleep, is the deepest and most refreshing phase. During stage-1 sleep, we are easily awakened; during delta sleep, the reverse is true. Unfortunately, delta sleep declines in the elderly (Kales A et al 1974). This age-related change in delta sleep may explain why sleep tends to be fragmentary in the elderly. Interestingly, there is little change throughout life in the amount of REM (rapid eye movement) sleep. REM sleep is the active phase of sleep where the brain is still very active.

Although they get less sleep and may waken exceptionally early, the elderly often suffer from daytime drowsiness because of this altered sleep architecture. Many think that older individuals simply require less sleep than others, however, there is no evidence to support this belief. The fact that older adults sleep less than younger adults do may actually reflect their inability, rather than their need, to sleep (Rajput V et al 1999).

### MELATONIN AND SLEEP

Melatonin is a hormone released by the pineal gland in response to the absence of light. Its release into the bloodstream triggers a chain of events that promotes sleep. It is well known for this role and may be used effectively as an oral supplement to help reentrain the sleep cycle in situations such as jet lag, in which the normal circadian rhythm of sleeping and waking gets out of sync with the local environment (Burgess HJ et al 2003; Eastman CI et al 2005; Erren TC et al 2004).

Melatonin production decreases during aging, and patients with Alzheimer’s disease exhibit a profound decrease in this important hormone. When Alzheimer’s patients are given melatonin orally, their sleep improves and the progression of cognitive impairment slows (Wang JZ et al 2006). The natural decline in melatonin may be the underlying cause of disturbances in sleep architecture among the elderly (Munch et al M 2005; Pandi-Perumal SR et al 2005).

Studies of its mechanism of action suggest that melatonin triggers a drop in body temperature through a complex interaction with the hypothalamic-pituitary-thyroid axis and by stimulation or suppression of certain corollary hormones, which in turn is associated with the onset of sleep. Melatonin is also believed to potentiate the effects of the neurotransmitter most associated with sleep and relaxation, gamma-aminobutyric acid (GABA), through direct interaction with GABA receptors (Atkinson G et al 2005; Mazzoccoli G et al 2004; Melatonin [monograph] 2005). More recent data indicate that melatonin may, in fact, be directly sleep-inducing (Zemlan FP et al 2005).

In light of the recent research demonstrating melatonin's many roles in the body, it seems that low levels of this hormone may actually be dangerous. For instance, there appears to be a relationship between the age-related decline in melatonin production and the decline in immune function that also accompanies old age. Known as immunosenescence, this phenomenon is associated with an increased incidence of cancer and infectious disease. As a result, some scientists have proposed that melatonin may be useful to enhance immunity and reduce the incidence and severity of these age-related maladies (Srinivasan V et al 2005). One researcher stated, "Chronic sleep loss could contribute to acceleration of the aging process" (Copinschi G 2005).

## **SLEEP HYGIENE**

Virtually everyone will struggle with insomnia on occasion. For instance, a 1995 poll of Americans found that 49 percent were dissatisfied with their sleep at least five nights each month (Ringdahl EN et al 2004). The first step to ensuring adequate sleep is to implement good sleep hygiene.

Sleep hygiene refers to a set of behaviors designed to encourage routine, restful sleep. These behaviors include some obvious elements, such as choosing a dark, quiet sleeping environment, avoiding caffeine or other stimulants (including nicotine) in the hours preceding bedtime, and keeping an unchanging bedtime-wake schedule. It is especially important to set a schedule and stick to it. Doctors recommend going to bed and rising at the same times every day, even on weekends. They also recommend reserving the bedroom for sleep; do not bring work to bed or watch television, for example.

Regular exercise is known to improve sleep (King AC et al 1997), but it should not be done immediately before retiring, when it may have a stimulating rather than a sedating effect. Experts also recommend finding ways to manage stress and reduce worries so that bedtime is a more relaxing experience (American Academy of Family Physicians 2005). Do not nap during the day if doing so seems to make it harder to fall asleep at night, and consider eating a tryptophan-rich snack before bedtime (e.g., whole-grain cereal with milk, yogurt with fresh fruit). Avoid foods, such as chocolate, that may contain caffeine.

Limit intake of alcohol. Although it may hasten sleep, evidence suggests that it interferes with deep, restful sleep (American Academy of Family Physicians 2005; Jefferson CD et al 2005; Landolt HP et al 2000). In fact, in one study of middle-aged men, a "moderate" dose of alcohol (defined as 0.55 g ethanol per kilogram of body weight) taken six hours before scheduled bedtime was enough to significantly alter the restfulness of sleep. Despite having zero breath-alcohol concentrations at bedtime, the men's sleep efficiency, total sleep time, stage 1, and REM sleep were all reduced. In the second half of the sleep episode, wakefulness increased twofold. Although they had metabolized and effectively eliminated the alcohol they had consumed in late afternoon, the men clearly suffered significant disruptions in subsequent sleep quality (Landolt HP et al 1996).

### ***Good sleep hygiene***

Getting a good night's sleep starts with good sleep hygiene. Experts recommend the following:

- Go to bed and rise at the same times every day, even on weekends.
- Maintain a bedtime routine, doing the same (relaxing) activities every night.
- Do not use the bed for anything but sleep and sex.
- Sleep in a dark, quiet room. If necessary, mask ambient noises with a fan or other "white-noise" generator. Or try earplugs.
- If you have not fallen asleep after 30 minutes, get up and sit quietly in another room. Do not fret about your lack of sleep. After 20 minutes, retire to bed again. Repeat as necessary. Known as stimulus control therapy, this approach to falling asleep helps reassociate the bedroom with restful sleep rather than stress over lack of sleep.
- Avoid caffeine, tobacco, and alcohol in the hours preceding bedtime.
- Exercise routinely during the day to improve onset and quality of sleep.
- Avoid napping during the day.

## **TRANSIENT INSOMNIA/CHRONIC INSOMNIA**

For some individuals, problems falling or remaining asleep become chronic. Defined as "inadequate quantity or quality of sleep that

has persisted for at least one month” (Rajput V et al 1999), chronic insomnia is often characterized by an individual’s primary complaint: Does the patient experience more difficulty falling asleep or staying asleep? Effective treatment of insomnia relies on understanding the causes of particular symptoms.

It should be noted that certain medical conditions, such as menopause, depression, allergies, arthritis, or benign prostatic hypertrophy, may affect sleep quality. Common medications may add to the problem. It may be prudent to address such underlying conditions before, or in addition to, addressing insomnia. Menopausal women, for example, may benefit from treatment with supplements such as black cohosh (*Cimicifuga racemosa*) or dong quai (*Angelica sinensis*), which may reduce hot flashes or anxiety, thus improving sleep (Chen SW et al 2004; Kupfersztain C et al 2003; Mahady GB 2005).

## DIFFICULTY STAYING ASLEEP

One subtype of chronic insomnia is typified by the inability to remain asleep throughout the night despite falling asleep with little or no difficulty. Chronic drug or alcohol abuse is one cause; depression and anxiety disorders are other potential causes. Breathing disorders are also linked with chronic insomnia. Upper airway resistance syndrome may interfere with restful sleep, and obstructive sleep apnea syndrome, which frequently occurs in obese patients, may be characterized by loud snoring, choking, or gasping episodes during sleep. These frequent nocturnal breathing interruptions fragment sleep. As a result, both conditions are accompanied by excessive daytime drowsiness.

Breathing disorders may require diagnosis in a sleep laboratory and may warrant special treatment. For instance, continuous positive airway pressure treatment (using a type of breathing mask) may be prescribed to treat sleep apnea. Such treatments may greatly improve sleep (Guilleminault C et al 2001). Sleep apnea patients should avoid any medications, such as sedatives or hypnotics that may depress the respiratory system. These include barbiturates (e.g., Seconal® and Nembutol®) and benzodiazepines (e.g., Valium®) (Rajput V et al 1999).

## NATURAL REMEDIES FOR INSOMNIA

Even with adequate sleep hygiene, many people—especially elderly people—still have trouble sleeping. Many doctors are quick to prescribe any of the dozens of medications that are currently used as potential sleep aids. While some of the newer generation of “sleeping pills” may be safer and less habit forming than older medications, natural remedies are a better first-line therapy.

**Valerian.** Preparations made from the roots of valerian (*Valeriana officinalis*) have long been relied on to hasten refreshing sleep. Controlled studies show that valerian decreases the amount of time it takes to fall asleep, as well as the subjective quality of sleep, compared to placebo. Valerian also improves quality of sleep; at least one study has shown that valerian increases the percentage of time participants spend in slow-wave sleep. This is significant because slow-wave sleep is considered the most profoundly refreshing sleep phase (Herrera-Arellano A et al 2001; Leathwood PD et al 1982, 1985; Trevena L 2004; *Valeriana officinalis* [monograph] 2004). One recent multicenter, double-blind, randomized parallel group study compared valerian, 600 mg/day, to the commonly prescribed tranquilizer oxazepam (Serax®). Valerian was at least as effective (Ziegler G et al 2002).

While valerian is generally considered safe (Krystal AD et al 2001), the same cannot be said of most hypnotic drugs. “Long-term use of hypnotic agents can become complicated by drug tolerance, dependence, or rebound insomnia,” noted one scientist (Kirkwood CK 1999). Prescription drugs such as Valium® may cause morning “hangover”: fogginess of the mind, lethargy, clumsiness, and other symptoms. Valerian has consistently been shown to have no such side effects. In a randomized, controlled, double-blind study, researchers administered 600 mg valerian extract to 102 participants. The following morning, participants’ reaction times, alertness, and concentration were evaluated. Researchers found no negative effects on any objective parameters of alertness or ability to concentrate subsequent to single or multiple doses of valerian (Kuhlmann J et al 1999).

More recently, researchers examined the effects of exceptionally high doses of valerian (up to 1800 mg) on parameters relating to “hangover” versus diazepam (Xanax®) or placebo. The researchers concluded that valerian extract had no significant effects on any of the dependent measures. In contrast, the prescription drug impaired cognitive performance and affected mood (Gutierrez S et al 2004).

Traditionally, patients have been advised to take valerian for up to two weeks before expecting it to become fully effective. It is unclear whether this is truly necessary, however, as the clinical evidence is contradictory (Hadley S et al 2003).

Valerian contains the amino acid GABA, which could directly cause sedation. GABA acts as a neurotransmitter involved in regulation of relaxation, anxiety, and sleep. Valerian is also known to interact with GABA already active in the brain. Valerian prompts the release of GABA and inhibits enzymes involved in GABA’s breakdown, thus further increasing levels of this “relaxation neurotransmitter” (Cavadas C et al 1995; Yuan CS et al 2004).

Although it does not regulate sale or production of valerian, the Food and Drug Administration (FDA) lists valerian as “Generally Recognized as Safe.” No significant drug interactions have been reported, although valerian might increase the sedating effects of

barbiturates or anesthetics drugs (Yuan CS et al 2004). It is also possible, but not definitively established, that valerian affects the metabolism of some other drugs in a manner similar to grapefruit (Donovan JL et al 2004; Lefebvre T et al 2004). Valerian has also been associated with liver damage, although purified extract of valerian appears to be safe for the liver.

Most published studies have found valerian effective for the treatment of insomnia when root extract equivalent to 300 to 600 mg is taken 30 minutes to two hours before intended bedtime. A study of valerian pharmacokinetics—the rate at which active constituents enter the bloodstream and are subsequently eliminated from the body—confirmed the effectiveness of this dosing regimen (Anderson GD et al 2005).

**L-tryptophan.** L-tryptophan is an amino acid that serves as a precursor for the neurotransmitter serotonin. Serotonin has been implicated in the regulation of sleep, depression, anxiety, appetite, sexual behavior, and body temperature (Birdsall TC 1998). In recent years, researchers have studied L-tryptophan's ability to help insomniacs. One study found that tryptophan depletion contributed to insomnia. The researchers gave 15 insomniacs an amino acid drink that depleted tryptophan, then studied the participants' sleep patterns. They found that sleep was significantly disrupted after tryptophan levels were lowered (Riemann D et al 2005). Another study comparing "protein-source" tryptophan, or tryptophan that comes from a protein, with pharmaceutical-grade tryptophan, which does not include protein, found they were equally effective in treating insomnia (Hudson C et al 2005). Previously, it was thought that protein-source tryptophan would be less effective because protein contains amino acids that interfere with tryptophan's transport into the brain.

**Lemon balm.** Lemon balm (*Melissa officinalis* L) is often paired with valerian. A recently published study of a combination of valerian and lemon balm for the treatment of restlessness and disordered sleep in children found "a distinct and convincing reduction in severity . . . for all symptoms in the investigators' and parents' ratings" (Muller SF et al 2006). About 81 percent of patients with sleep disorders experienced improvement of their symptoms after taking the study preparation.

Lemon balm appears to work by reducing anxiety. A recent double-blind, placebo-controlled, randomized, balanced crossover experiment showed that a 600-mg dose of lemon balm improved the negative mood effects of a standardized procedure designed to induce stress under laboratory conditions. Participants taking lemon balm had "significantly increased self-ratings of calmness," noted the researchers. "In addition, a significant increase in the speed of mathematical processing, with no reduction in accuracy, was observed after ingestion of the 300-mg dose" (Kennedy DO et al 2004).

## PRESCRIPTION SLEEP AIDS

Ideally, prescription drugs are not necessary for sleep aid. Some of these medications carry a risk of tolerance. In other words, it requires more and more of the medication to get a good night's rest. Another side effect is daytime drowsiness caused by lingering effects from the previous night's medication. Worse yet, many of these medications are addictive in the sense that patients lose the ability to sleep without them.

However, if natural remedies fail to bring about refreshing sleep, it is Life Extension's position that people should use whatever means are available to them, including prescription medications, to get good sleep. Sleep medications may be classified into the following categories:

**Benzodiazepines.** These drugs were introduced in the 1960s and were used for the treatment of insomnia. They were very popular sleep aids for several decades but are prescribed less frequently today because of concerns over dependency, impairment in memory and movement, and a "hangover" effect the next day. The following are some popular benzodiazepines:

- Valium® (diazepam)
- Dalmane® (flurazepam)
- Doral® (quazepam)
- Halcion® (triazolam)
- ProSom® (estazolam)
- Restoril® (temazepam)
- Klonopin® (clonazepam)

**Nonbenzodiazepine, benzodiazepine receptor agonists.** Introduced in the 1990s and sometimes referred to as "Z drugs," these drugs are now the first-line treatment for insomnia. They include Ambien® (zolpidem) and Sonata® (zaleplon). These drugs have been shown to reduce the time it takes to fall asleep and have fewer side effects than the benzodiazepines, but they are also recommended for short-term use. A newer drug in this class, Lunesta® (zopiclone), appears to be equally effective and may be acceptable for long-term therapy. In general, however, most researchers call for better long-term studies.

Other drugs used to treat insomnia include sedative antidepressants, such as trazodone (Desyrel®), amitriptyline (Elavil®) and doxepin (Sinequan®). These medications are usually prescribed for insomnia in the context of depression rather than for treatment

of primary insomnia, at least in part because of their many side effects, including dry mouth, weight gain, constipation, and a host of other problems. A typical dose of Elavil® taken a few hours before bedtime is 10 to 25 mg. Some people use Elavil® until the side effects become too pronounced and then discontinue it for months or years.

One way of avoiding the tolerance problem is to alternate the type of sleeping pill used. Here is a suggested prescription drug schedule to treat chronic insomnia for the person who has never taken prescription sleeping pills:

1. Valium, 2.5 mg, taken only at bedtime for 30 days
2. During the next 30-day cycle, 5 to 10 mg Ambien® taken only at bedtime
3. During the next 30-day cycle, 1 to 3 mg Klonopin® taken only at bedtime

At some point, patients may find that they do better by taking Valium® one night, Ambien® the next night, and Klonopin® or Lunesta® the third night. The drug Sonata® in a 5 to 10 mg dose provides about 5 hours of sleep and can be helpful on occasions when only a limited amount of sleep time is available. If heavy alcohol is consumed, these types of drugs should be avoided on the same night. It should be noted that chronic alcohol intake in and of itself is a major cause of poor sleep patterns.

A person with chronic insomnia must develop a close relationship with a physician who understands that some people need sleep medications on a routine basis or their lives will be miserable and that they are also at a higher risk of contracting a serious degenerative disease.

Low-dose melatonin may help any of these prescription drugs work more effectively.

### LIFE EXTENSION FOUNDATION RECOMMENDATIONS

Chronic insomnia is best approached by behavior modification and natural therapies before turning to prescription drugs. The following lifestyle changes may relieve insomnia:

- Avoid caffeine at least six hours before bedtime.
- Avoid alcohol or smoking for two hours before bedtime.
- Get regular exercise, but do not exercise within three hours of bedtime.
- Establish regular bedtime and waking hours.
- Do not work in the bedroom.
- Consider using white-noise generators or relaxing music to “turn off” your mind.

If sleep is disrupted by another condition, such as restless legs syndrome, painful arthritis, or carpal tunnel syndrome, it may be helpful to seek treatment for that condition. In addition, the following herbs and supplements have been shown to help induce sleep:

- **Valerian**—300 to 600 milligrams (mg) valerian root 30 minutes to two hours before bedtime. If taking liquid valerian, take 30 to 40 drops of extract in a small amount of warm water within the hour before bedtime. Long-term valerian therapy is not recommended. Valerian is sometimes used with lemon balm.
- **Melatonin**—300 micrograms (mcg) to 10 mg about 30 minutes before bedtime. Sometimes lower doses work better than higher doses.
- **GABA**—350 to 700 mg before bedtime (taken sublingually)
- **L-tryptophan**—1500 to 2000 mg before bedtime

If natural sleep remedies do not restore refreshing sleep, pharmaceutical drugs are available, including Klonopin®, Ambien®, Lunesta®, and many others. These drugs must be prescribed by a physician.

In addition, dehydroepiandrosterone (DHEA) replacement therapy may be recommended. Almost all aging humans are deficient in DHEA, and DHEA may help reduce cortisol levels and produce a feeling of well-being. Although DHEA has not been studied in insomnia, a suggested starting dose of 15 to 75 mg, followed by blood testing after three to six weeks, is recommended to promote peace of mind. It is important to take DHEA in the morning as taking it at night can be stimulatory.

### PRODUCT AVAILABILITY

All the nutrients and supplements discussed in this section are available through the Life Extension Foundation Buyers Club, Inc. For ordering information, call anytime toll-free 1-800-544-4440, or visit us online at [www.LifeExtension.com](http://www.LifeExtension.com).

The blood tests discussed in this section are available through Life Extension National Diagnostics, Inc. For ordering information, call anytime toll-free 1-800-208-3444, or visit us online at [www.LifeExtension.com](http://www.LifeExtension.com).

## INSOMNIA SAFETY CAVEATS

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

### L-Tryptophan

- Do not take L-tryptophan if you have carcinoid tumors.
- Do not take L-tryptophan while taking monoamine oxidase inhibitors (MAOIs) (type A) or within 2 weeks of discontinuing MAOIs.
- Do not take L-tryptophan with any antidepressant medications, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants or MAOIs.
- Do not take L-tryptophan with serotonin 5-HT receptor agonists, including naratriptan, sumatriptan and zolmitriptan.
- Do not take L-tryptophan if you have ischemic heart disease (e.g., a history of myocardial infarction, angina pectoris or documented silent ischemia), coronary artery spasm (e.g., Prinzmetal's angina), uncontrolled hypertension or any other significant cardiovascular disease.
- L-tryptophan can trigger excess serotonin formation in tissues other than the target organ and cause significant adverse reactions.
- L-tryptophan can cause nausea, diarrhea, loss of appetite, vomiting, difficulty breathing, pupil dilation, abnormally sensitive reflexes, loss of muscle coordination, blurry vision and cardiac dysrhythmia.

### Melatonin

- Do not take melatonin if you are depressed.
- Do not take high doses of melatonin if you are trying to conceive. High doses of melatonin have been shown to inhibit ovulation.
- Melatonin can cause morning grogginess, a feeling of having a hangover or a "heavy head," or gastrointestinal symptoms such as nausea and diarrhea.

For more information see the Safety Appendix

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