Adequate sleep is essential for healthy functioning of the 75 trillion cells that comprise the human body. Sleep disorders are a common complaint and can make a great impact on quality of life. Common sleep disorders include primary insomnia, restless legs syndrome (RLS), and sleep-disordered breathing. Other factors such as illness, medications, and psychosocial problems also contribute to development of sleep disorders. According to the 2002 National Health Interview Survey analysis, more than 1.6 million adult Americans use complementary and alternative medicine (CAM) to treat insomnia or trouble with sleeping.1

Healthy sleep includes two types that alternate throughout the night. The first type is known as slow-wave sleep, or non–rapid eye movement (REM) sleep, and comprises approximately 75% of total sleep. The second type is REM sleep, which comprises 25% of total sleep, lasts 5–30 minutes, and usually recurs approximately every 90 minutes. REM sleep is characterized by an increase in brain activity with active dreaming, decreased muscle tone, variable heart and respiratory rates, and REMs.

Normal sleep stages show a progression of changes in brain waves. Stages 1 and 2 are considered to be light sleep, and stages 3 and 4 are deep or slow-wave sleep. As stage 1 of sleep progresses, alpha waves decrease and are replaced by bursts of alpha-wave sleep spindles and then are replaced by theta waves in stages 2 and 3. Stage 4 is characterized by a predominance of delta waves (which also occur during a significant percentage of stage 3), followed by REM sleep, which produces beta waves, similar to those of an alert and awake person.

Sleep is controlled internally by homeostatic and circadian processes such as increased melatonin secretion from the pineal gland; cortisol secretion is low, and core body temperature is decreased.

Sleep appears to be important for processing memories and newly learned tasks, as changes are seen in sleep architecture following the acquisition of a simple motor learning task.2 In addition, the different sleep stages are involved in the consolidation of different types of memories. Slow-wave sleep benefits mainly the consolidation of declarative memories such as facts and episodes, while REM sleep improves emotional memories and procedural memories for skills.3

Insomnia

Insomnia is the most commonly reported sleep problem. Symptoms of insomnia include difficulty in initiating sleep, difficulty in maintaining sleep, waking up too early, and non-restorative or poor quality of sleep. Circadian-rhythm abnormalities can result in phase-delay sleep, phase-advance sleep, a sleep–wake cycle longer than 24 hours, or variations in the sleep–wake cycle. Additional diagnostic criteria may include perceived daytime impairment or distress as a function of the insomnia symptoms, insomnia symptoms persisting for at least 1 month, and symptoms that do not occur exclusively in the presence of another sleep disorder, mental disorder, or the direct physiologic effects of a substance or medical condition.4

Although insomnia can be a primary condition, it can also be considered secondary to other disorders. Studies show that abnormal sleep patterns predict lower life expectancy, and individuals with insomnia are more likely to develop mood disorders, substance abuse, and other adverse health conditions.

The estimates regarding the prevalence of insomnia vary widely as a result of inconsistent diagnostic criteria. Currently, it is believed that 10%–15% of the adult popula-
tion has chronic insomnia, and an additional 25%–35% has transient or occasional insomnia. Risk factors include age and gender, with an increased prevalence in women and elderly people.

Elderly people, in particular, are affected, and one study showed that 34.2% of elderly participants admitted to having problems with sleep, but only 20.3% fulfilled the criteria for primary insomnia. This study also correlated the existence of an anxiety disorder, lower life satisfaction, and consumption of psycho-pharmaceuticals with insomnia.

Pain also plays an important role in sleep quality. For example, the prevalence of insomnia symptoms and nonrefreshing sleep in persons with arthritis was 24.8% and 11.9%, respectively. Conditions included arthritis or rheumatism, excluding fibromyalgia. These estimates are twice as high as those for persons without arthritis. In fact, more than 40% of individuals with insomnia symptoms reported at least one chronic painful physical condition. The presence of a chronic painful physical condition was also associated with a shorter sleep duration and more frequent difficulty with sleep or inability to resume sleep once the person was awake.

Hypnotic medications are the most frequently prescribed conventional treatment for insomnia. Pharmacotherapy includes benzodiazepine-receptor agonists and nonbenzodiazepine hypnotics, which are the drugs of choice for this disorder. Many hypnotics, such as benzodiazepines, are agonistic modulators of gamma-aminobutyric acid (GABA) receptors. Such compounds increase the ability to fall and stay asleep, but inhibit REM and deep non-REM sleep. Cognitive-behavioral therapy has been shown to be just as effective as hypnotic medications for treating acute insomnia and more effective for treating chronic insomnia.

Restless Legs Syndrome

RLS is a neurologic condition that is defined by an irresistible urge to move the legs, which develops at rest and compels the person to move, particularly at night. The prevalence of RLS in Western countries is an estimated 7%–11% of the population. RLS has a higher prevalence in pregnancy, end-stage renal disease, iron-deficiency anemia, and attention deficit hyperactivity disorder (ADHD). Primary RLS is familial in up to two thirds of affected patients.

It is currently hypothesized that the pathology of RLS involves systemic or brain–iron deficiency along with impaired dopaminergic neurotransmission in the brain. Studies indicate that sleep latency was longer, sleep efficiency was lower, and periodic leg movement index was higher in patients with RLS. With cerebrospinal fluid (CSF) examination, iron and ferritin values were lower and transferrin values were higher in an RLS group compared with individuals without RLS, suggesting low brain–iron concentration caused by the dysfunction of iron transportation from serum to the central nervous system (CNS) in these patients. Current conventional treatment for RLS includes dopamine agonists and possibly anticonvulsant and opioid medications.

Sleep-Disordered Breathing

Sleep-disordered breathing is a general category of sleep disorders that includes snoring, upper-airway resistance syndrome, and sleep apnea. Approximately half of patients with sleep-disordered breathing also experience insomnia. Sleep apnea is defined as a sleep disorder with frequent episodes of upper-airway obstruction or insufficient neurologic respiratory stimulation with hemoglobin oxygen desaturation. The condition is characterized by the occurrence of breathing cessation (apnea) and periods of reduced breathing (hypopnea). Sleep apnea increases morbidity and mortality. Obstructive sleep apnea (OSA) is the most common type and is characterized by a lack of airflow, despite respiratory effort, caused by obstruction in the upper airway. In industrialized countries, OSA affects approximately 4% of men and 2% of women.

OSA increases with age, and studies suggest the condition may occur in as high as 31% of elderly men and 19% of elderly women. Studies show that habitual snoring affects 29.5% of males and 8.9% of females. Studies have indicated that sleep apnea is more common in men and increases with age. In addition, sleep apnea is more frequent in African Americans than in Caucasian Americans.

Males who snore and who are over age 40, are obese, smoke, or use alcohol are at increased risk for OSA. Studies indicate that both elevated body mass index (BMI) and increased neck circumference increase risk for sleep apnea. The strongest predictor for OSA is obesity. Studies show that the risk of OSA increases fourfold with an increase of the BMI by 1 standard deviation. Neck circumference is also a strong predictor, suggesting that upper body or central obesity is more predictive than generalized obesity.

Hypothyroidism and menopause have also been associated with increased risk of OSA. OSA is an independent risk factor for several conditions such as systemic hypertension, cardiovascular disease, stroke, and abnormal glucose metabolism. Conventional therapy for sleep apnea involves the use of a continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) unit at night or dental appliances that help correct anatomical anomalies.

The Impact of Sleep Disorders

Sleep disorders impair general physical and cognitive functioning. These disorders can diminish quality of life, contribute to accidents, and lead to problems at work. Insomnia is frequently associated with other physical and mental conditions, either as a consequence or a contributing factor. In particular, research supports a strong association between insomnia and depression.

One study showed that approximately 28% of individuals with insomnia had current diagnoses of mental disorders, and more than 25% had histories of psychiatric problems. In most of the cases of individuals with mood disorders, insomnia appeared before or around the same time as the mood disorder symptoms. This study also showed that psychiatric history is closely related to the severity and chronicity of current insomnia. In addition, chronic insomnia can be a residual symptom...
of a previous mental disorder and may put these individuals at a higher risk of relapse.22

Sleep deficits cause a range of neurobehavioral changes, including depressed mood, lapses of attention, slowed working memory, and reduced cognitive processing. Neurobehavioral deficits will accumulate across days of partial sleep loss. Recent research indicates that significant daytime cognitive dysfunction accumulates to levels comparable with that found after total sleep deprivation following days of chronic restriction of sleep duration below 7 hours per night. In addition, studies

with healthy adults subjected to sleep restriction have found adverse health effects on endocrine functions and metabolic and inflammatory responses, demonstrating that sleep restriction produces undesirable physiologic consequences.23

According to one survey, 30% of respondents reported currently experiencing sleep problems. Compared with respondents who did not have sleep problems, respondents who reported sleep problems were found to have worse general functioning in areas such as cognitive functioning and energy; more work-related problems, including decreased job performance, lower job satisfaction, and increased absenteeism; and a greater likelihood of comorbid physical and mental health conditions.24

Research has shown that the increased occurrence of accidents in people with insomnia poses a significant public safety risk. A study conducted with professional drivers demonstrated that accident risk significantly increased with frequent snoring and daytime sleepiness.25 Additional research has shown an increased risk of vehicular crash involvement with sleep-onset insomnia, frequent tiredness, and related conditions such as anxiety and depression.26

**Lifestyle Factors**

Lifestyle factors play a significant role in sleep disorders. In one study, sleep hygiene practices were compared between individuals with insomnia and healthy controls. This study measured sleep hygiene practices such as cigarette smoking, smoking near bedtime, alcohol use, caffeine use, napping, time in bed, and reported likelihood of sleepiness on weekends. Individuals with insomnia reported poorer sleep hygiene compared with healthy controls. In particular, people with insomnia reported an increase in prevalence of smoking close to bedtime, increased use of alcohol, more naps per week, and sleeping-in on days not worked.27 In addition, insomnia rates are higher in individuals who are divorced, separated, or widowed; are less educated, have lower domestic income, or are unemployed; who work nights or do shift work; or who have poor night routines, such as going to sleep too early, reading or watching television when going to bed, or eating late in the evening.28

Several lifestyle changes also can make a significant reduction in the severity of sleep apnea. Weight loss is important because of the relationship between increased BMI and neck circumference and OSA. Patients should be educated to sleep lying on their sides and to avoid alcohol and sedatives.

**Stress**

The hypothalamic–pituitary–adrenal (HPA) axis plays a significant role in sleep disorders.

Research indicates that both the diagnosis of insomnia and the severity of the sleep disturbance are related to overactivity of the HPA axis and increased secretion of cortisol. This overactivity of the HPA axis may be the common risk factor for insomnia and mental disorders such as anxiety and depression. HPA axis and corticotropin-releasing factor (CRF) dysregulation and overactivity are believed to mediate both depression and insomnia.29

Research has shown that patients with insomnia have significantly increased evening and nocturnal cortisol levels, and evening cortisol levels have been correlated with number of nocturnal awakenings.30 In one study, people with insomnia had significantly higher 24-hour adrenocorticotropic hormone (ACTH) and cortisol secretions compared with normal controls. Within the 24-hour period, the greatest elevations were observed in the evening and first half of the night.

In another study, people with insomnia with a high degree of objective sleep disturbance compared with those with a low degree of sleep disturbance secreted a higher amount of cortisol. The authors of this study concluded that insomnia is associated with an overall increase of ACTH and cortisol secretion, which retains a normal circadian pattern.31

Other researchers have shown that patients who report chronic insomnia may have a more general disorder of hyperarousal as shown by an increase in 24-hour metabolic rate, which may also play a role in symptoms.32

**Caffeine**

In a double-blind placebo-controlled crossover study, the effects of caffeine on daytime sleep after a night of total sleep deprivation were investigated to examine the theory that patients with insomnia would be more affected by caffeine administration. During the baseline night, patients with insomnia had significantly less delta sleep and less total sleep time than healthy controls. After 1 night of total sleep deprivation, subjects were given caffeine. The patients with insomnia had significantly longer sleep latency and less total sleep time compared with normal volunteers demonstrating that these patients had a higher sensitivity to the diurnal awakening effect of caffeine.

The researchers in this study suggest that changes in the adenosine receptors could be partially responsible for the hyperarousal state that has been reported in primary insomnia.33
Natural Supplements for Sleep Disorders

Melatonin

With age, melatonin production declines and the prevalence of sleep disorders, particularly insomnia, increases. In both young and elderly individuals with primary insomnia, nocturnal plasma melatonin levels tend to be lower than those in healthy controls. Studies have shown that melatonin therapy may be beneficial for ameliorating insomnia symptoms in circadian-rhythm sleep disorders, such as delayed sleep-phase syndrome, in which melatonin can advance the phase of the sleep–wake rhythm significantly.34

Melatonin supplementation reportedly induces drowsiness and sleep and may ameliorate sleep disturbances, particularly the nocturnal awakenings associated with old age. A meta-analysis of studies investigating the efficacy of melatonin for insomnia was performed. Melatonin treatment significantly reduced sleep-onset latency, increased sleep efficiency, and increased total sleep duration.35

In a randomized double-blind placebo-controlled trial, 3 mg or 6 mg of melatonin (depending on body weight) or placebo was given for 4 weeks to children with attention-deficit/hyperactivity disorder (ADHD) and chronic sleep-onset insomnia. Melatonin advanced circadian rhythms of the sleep–wake cycle and enhanced total time asleep in children with ADHD and chronic sleep-onset insomnia.36

In another similar study, 3 mg of melatonin was used to treat insomnia associated with schizophrenia. Melatonin significantly improved the quality and depth of night-time sleep, reduced the number of night-time awakenings, and increased the duration of sleep without producing a morning hangover compared with placebo. In addition, melatonin significantly reduced sleep-onset latency, heightened freshness on awakening, improved mood, and improved daytime functioning, according to subjective reports.37

In a randomized double-blind placebo-controlled study, the efficacy and safety of a prolonged-release melatonin 2-mg formulation (1 tablet per day taken 2 hours before bedtime) were examined in patients with insomnia ages 55 years and older. The patients had a significant shortening of sleep latency to the same extent as that produced by most frequently used sleep medications. Reported quality of life also improved significantly. The researchers concluded that melatonin supplementation resulted in significant improvements in sleep quality, morning alertness, sleep-onset latency, and quality of life in patients with primary insomnia who were 55 or older.38

5-Hydroxytryptophan and 5-Hydroxytryptophan

5-Hydroxytryptophan (5-HTP) is the intermediate metabolite of the essential amino acid L-tryptophan in the biosynthesis of the neurotransmitter serotonin. Both L-tryptophan and 5-HTP have been used to help patients who have sleep and mood disorders such as depression. In particular, 5-HTP has been shown to improve sleep quality by increasing the amount of REM sleep.39 L-tryptophan produces an increase in rated subjective sleepiness and a decrease in sleep latency (time to sleep). L-Tryptophan may have additional effects such as a decrease in total wakefulness and/or an increase in sleep time. The best results, in terms of positive effects on sleep, have been found in patients with mild insomnia or in normal individuals reporting longer-than-average sleep latency.40

In one study, the effects of L-tryptophan depletion were evaluated with polysomnography in patients with primary insomnia. Evaluation of sleep parameters showed an increase in percent sleep-period time (SPT) during stage 1 and a decrease in percent SPT during stage 2. REM density, a measure of the frequency of REMs during REM sleep, was increased after the L-tryptophan depletion, compared with baseline. The researchers concluded that L-tryptophan depletion has a negative impact on sleep continuity and a stimulating effect on phasic measures of REM sleep in patients with primary insomnia. Percent SPT was increased in stage 1, whereas percent SPT was decreased in stage 2. Indices of phasic activity of REM sleep (REM density) were increased after the L-tryptophan depletion.41

In another clinical trial, the effects of 3 g of L-tryptophan on sleep, performance, arousal threshold (the ease with which a sleeping person is awakened), and brain electrical activity during sleep were evaluated in individuals with chronic sleep-onset insomnia. The results showed no effect of L-tryptophan on sleep latency during the first 3 nights of supplementation. However, sleep latency was significantly reduced on nights 4–6 of L-tryptophan supplementation. Unlike benzodiazepine hypnotics, L-tryptophan did not alter sleep stages, impair performance, elevate arousal threshold, or alter brain electrical activity during sleep.42

A similar study used 2 g of L-tryptophan in patients with severe chronic insomnia for 4 weeks. A second 4-week period without L-tryptophan was used as a control. The results indicated that 76% of patients had a markedly improved sleeping pattern after 4 weeks. According to self-rating reports, sleep improved significantly between the 10th and 15th day after beginning treatment.43

L-Theanine

L-Theanine is an amino acid found in high concentrations in Camellia sinensis (green tea). Research indicates that L-theanine supplementation produces some relaxing effects.44 Animal
studies suggest that L-theanine increases brain serotonin, dopamine, and GABA levels. A small study showed that 200 mg of L-theanine increased alpha-brain wave activity and induced a sense of relaxation.

Studies using animal models have shown that L-theanine causes dopamine release from dopaminergic neurons and may inhibit excitatory neurotransmission and cause inhibitory neurotransmission, suggesting a possible mechanism for this amino acid’s anxiolytic activity.

In a double-blind placebo-controlled study, L-theanine was evaluated for potential influence on psychologic and physiologic states under stress. Participants underwent four separate trials: one in which they took L-theanine at the start of an experimental stress task, one in which they took L-theanine midway, and two control trials in which the participants either took a placebo or nothing. The results showed that L-theanine intake resulted in a reduction in heart rate and salivary immunoglobulin A responses to an acute stress task relative to placebo, which is likely to be attributable to an attenuation of sympathetic-nervous system activation. Although direct evidence is lacking, modulation of the stress response may reduce insomnia symptoms.

**Gamma-Aminobutyric Acid**

GABA is the main inhibitory neurotransmitter of the CNS. It is well-established that activation of GABA(A) receptors favors sleep. In one study, electroencephalograms (EEGs) after 60 minutes of GABA administration showed significantly increased alpha waves and decreased beta waves. These findings suggest that GABA not only induces relaxation but also reduces anxiety.

**Vitamins and Minerals for Sleep**

Various vitamins and minerals have been shown to benefit patients with select sleep disorders. For example, research has shown that administration of vitamin B12 may normalize human sleep–wake rhythm disorders such as non–24-hour sleep–wake syndrome, delayed sleep–phase syndrome, or insomnia.

Several nutrients have also been shown to benefit patients with RLS. Patients with this disorder have lower levels of dopamine. Iron is a cofactor in dopamine production and is integral in the etiology of RLS. Folic-acid supplementation has also been shown to reduce symptoms and may play a role in treating primary RLS.

In one study, iron, ferritin, and transferrin in both serum and CSF of patients with RLS was evaluated based on the hypothesis that iron deficiency in the CNS causes RLS symptoms as a result of the dysfunction of the dopaminergic systems. Polysomnographic sleep measures and subjective evaluation of sleep quality were also evaluated and compared between patients with idiopathic RLS and patients with psychophysologic insomnia without RLS symptoms.

An analysis of sleep patterns showed that sleep latency was longer, sleep efficiency was lower, and periodic leg-movement index was higher in the RLS group compared with the non-RLS group. Serum examination showed no significant differences for iron, ferritin, and transferrin values between the two groups. However, CSF examination showed that iron and ferritin values were lower and transferrin values were higher in the RLS group than those in the non-RLS group. These results suggest that low brain–iron concentration may be caused by the dysfunction of iron transportation from serum to CNS in patients with idiopathic RLS.

In a small study, oral magnesium therapy was investigated for its effect on symptoms in patients with moderate RLS over 4–6 weeks. Following magnesium supplementation, periodic limb movements during sleep associated with arousals decreased significantly. Periodic limb movements during sleep without arousal were also moderately reduced, thus demonstrating improvement in sleep efficiency. Magnesium has also been shown to produce antidepressant and anxiolytic-like effects.

**Botanicals for Sleep**

**Valerian**

*Valeriana officinalis* (valerian) is a frequently used botanical for both sleep and mood disorders. Research into physiologic activity of individual components has demonstrated direct
sedative effects and interaction with neurotransmitters such as 
GABA. The pharmacologic effects of valerian extract and the 
constituent valerenic acid have been shown to modulate the 
GABA(A) receptor.54

In a double-blind, randomized parallel study, adult patients 
diagnosed with nonorganic insomnia were treated with either 
600 mg of valerian extract or 10 mg of the benzodiazepine 
oxazepam for 6 weeks. Sleep quality was evaluated after the 
6 weeks: 600 mg of valerian extract was at least as efficacious 
as the treatment with 10 mg of oxazepam. Both treatments 
markedly increased sleep quality compared with baseline. In-
vestigators and patients reported similar effects of both treat-
ments. Mild-to-moderate adverse events occurred in 28.4% of 
patients who took the valerian extract and 36% of patients who 
took oxazepam. In addition, 82.8% of patients in the valerian 
group and 73.4% of patients in the oxazepam group rated their 
treatment as very good.55

Additional trials have shown that valerian supplementation 
produced a significant decrease in subjectively evaluated sleep-
latency scores and a significant improvement in sleep quality. 
Sleep quality improvement was most notable among smokers, 
people who considered themselves poor or irregular sleepers, and 
people who thought they normally had long sleep latencies.56

In a small randomized double-blind placebo-controlled crossover study, single-dose and long-term (14 days with mul-
tiple dosages) use of a valerian extract was evaluated on both 
objective and subjective sleep parameters in patients with pri-
mary insomnia. After a single dose of valerian, no objective or 
subjective effects on sleep were noted. However, after multiple-
dose treatment, sleep efficiency showed a significant increase 
on polysomnographic testing for both the placebo and the 
valerian groups, in comparison with baseline polysomno-
graphy. Compared with placebo, valerian reduced slow-wave sleep 
lateness. The slow-wave sleep percentage of time in bed was 
increased after long-term valerian treatment in comparison to 
baseline. In addition, a tendency for shorter subjective sleep 
latency was observed in patients who took valerian.57

In another study, a combination of valerian and 
Humulus lupulus (hops) was given to 30 patients with mild-to-moder-
ate, nonorganic insomnia. The patients were treated with 
500 mg of valerian extract and 120 mg of hops extract in the 
evening. Reexamination after 2 weeks with polysomnography 
revealed a decline in sleep latency and wake time, showing in-
creased sleep efficiency. Sleep stage 1 was reduced and slow-
wave sleep increased. Patients reported an improvement after 
2 weeks of treatment.58

Lemon balm
Melissa officinalis (lemon balm) is a botanical medicine with 
mild calming effects and the ability to reduce alertness.59 Brain 
function may be directly affected, as the terpenes in the essen-
tial oils of lemon balm are thought to act on some of the inhib-
itory neurotransmitters (such as GABA) in the brain, thereby 
producing a calming effect.60 A study using both valerian and 
lemon balm produced improvements in the amounts and qual-
ity of sleep in subjects who took this herbal combination.61 In

another study, an herbal combination of valerian and lemon 
balm was given to 918 children less than 12 years old who had 
restlessness and dyssomnia. The researchers found that 80.9% 
of the children who had dyssomnia experienced improvement 
and that 70.4% of the patients with restless improved.62

Passionflower
Passiflora incarnata (passionflower) has been used histori-
cally to treat anxiety and insomnia and was formerly approved 
as an over-the-counter (OTC) sedative and sleep aid in the 
United States. Although studies are lacking regarding the effi-
cacy of passionflower for sleep disorders, research does indicate 
that the herb is an effective anxiolytic that may be beneficial in 
insomnia-related sleep disorders.

In a double-blind randomized trial, the efficacy of passion-
flower extract was compared with the benzodiazepine oxaze-
pam in the treatment of generalized anxiety disorder. Passion-
flower extract and oxazepam were both effective in the treat-
ment of anxiety and no significant difference was observed 
between the two protocols. Oxazepam produced a more rapid 
onset of action but with significantly more job-performance 
impairment, suggesting that passionflower extract is an effec-
tive alternative for managing generalized anxiety disorder.63

Conclusion

Sleep disorders are a common complaint and affect a sub-
stantial percentage of the population. Whether as monothera-
pies, or as part of integrative treatment plans, natural ther-
apies and lifestyle modification have shown efficacy in manag-
ing many of the various causes of sleep disorders. It is the sleep 
cycle of each day that allows the body to undergo its “rest-
oration” process. Thus, enhancing the quality and quantity of 
sleep establishes the foundation for both the mind and body to 
maintain, regain, and sustain the 75 trillion cells that comprise 
the human body. The utilization of the most natural and least 
intrusive approaches to support optimal sleep and to sustain 
biochemistry and lifestyle habits is essential in the pursuit of 
wellness and healthy aging.

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