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Insomnia and Sleep/Wake Cycle Disorder

The importance of quality sleep in the functioning of the human brain and body cannot be overstated; without it, severe psychological and physiological consequences occur. Simply stated, sleep is an essential aspect of health. Many different physiologic processes occur during sleep, but perhaps the most important are the increased secretion of growth hormone, enhanced immune function, and the scavenging of free radicals in the brain.

Most people can tolerate a few days without much sleep and fully recover. However, chronic sleep deprivation appears to accelerate aging of the brain, causes neuronal damage, and leads to nighttime elevations in cortisol—further worsening sleep quality. It is estimated that the prevalence for insomnia may be as high as 50% of the adult population, with about 15% suffering from chronic insomnia and an additional 35% having transient or occasional insomnia.

NORMAL SLEEP PATTERNS

Normal adult sleep-wake patterns repeat themselves on an approximately 24-hour cycle, of which sleep constitutes one third. Exactly how much sleep is required varies from one person to the next. Sleep tends to decrease with age, but whether this tendency is a normal or abnormal progression is unknown. A 1-year-old baby requires about 14 hours of sleep a day, a 5-year-old about 12 hours, and adults about 7 to 9 hours. Women tend to require more sleep than men. The elderly tend to sleep less at night, but doze more during the day than younger adults.

From observation of eye movement and electroencephalographic (EEG) recordings, sleep is divided into two distinct types of sleep: rapid eye movement (REM) sleep and non-REM (NREM) sleep. During REM sleep the eyes move rapidly and dreaming takes place. When people are awakened during NREM sleep, they report that they were thinking about everyday matters, but rarely report dreams.

NREM sleep is divided into stages 1 through 4 according to level of EEG activity and ease of arousal. *(See Figure 1)* Deep sleep occurs during stages 3 and 4. Spending sufficient time in this stage is critical to overall sleep quality. As sleep progresses there is a deepening of sleep and slower brain wave activity

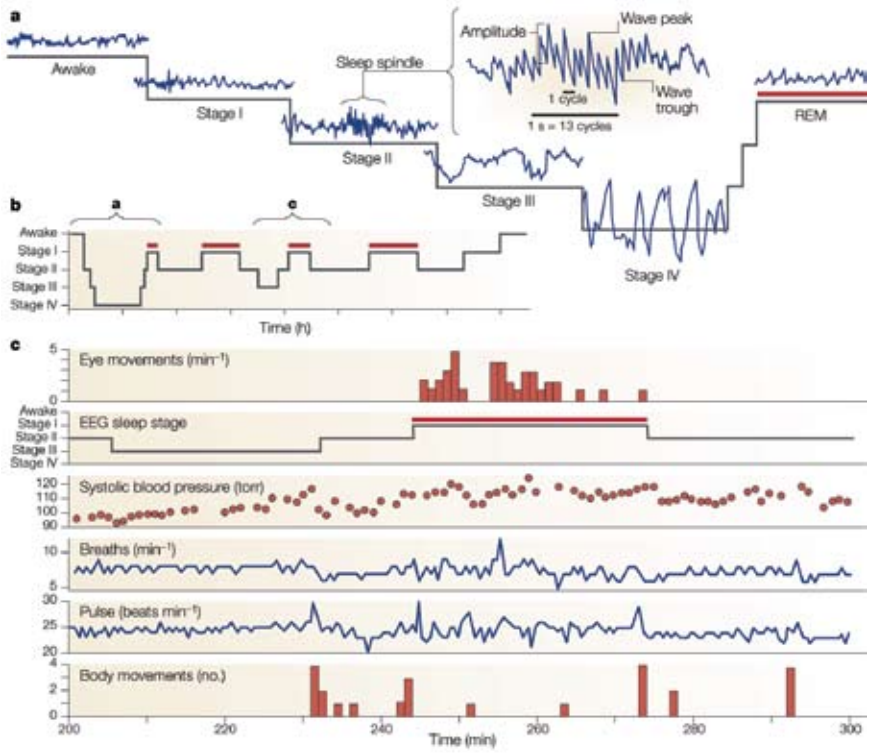

Figure 1* **Sleep-cycle basics.** NREM and REM sleep alternate in each of the four or five cycles that occur in each night of adult human sleep. Early in the night, NREM sleep is deeper and occupies a disproportionately large amount of time, especially in the first cycle, when the REM epoch might be short or aborted. Later in the night, NREM sleep is shallow, and more of each cycle is devoted to REM (red bars). Panel **b** illustrates these changes over the course of a night's sleep. Panel **a** depicts, in detail, features of an early-night sleep cycle in which NREM reaches its greatest depth at stage III and IV (delta) sleep, whereas panel **c** depicts a late-night cycle in which NREM descends only to stage III. The constant period length of the NREM-REM cycle indicates that it is timed by a reliable oscillator (for a discussion of ultradian alternation of REM and NREM sleep, see the main text), the amplitude of which varies according to extrinsic factors.

The cyclic organization of sleep varies within and between species. The period length of each REM-NREM epoch increases with brain size across species, and the depth and proportion of the NREM phase in each cycle increases with brain maturation within species. NREM sleep complexity is a function of brain systems, such as the thalamocortical circuitry, that reach their maximum development in mature humans only to decline in post-mature age. It can therefore be concluded that the differentiation of sleep is a function of brain differentiation, a rule that indicates both mechanistic and functional links between sleep and other brain functions.

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until REM sleep, when suddenly the brain becomes much more active. In adults, the first REM sleep cycle is usually triggered 90 minutes after going to sleep and lasts about 5 to 10 minutes. After the flurry of activity, brain wave patterns return to those of NREM sleep for another 90-minute sleep cycle.

Each night, most adults experience five or more sleep cycles. REM sleep periods grow progressively longer as sleep continues; the last sleep cycle may produce a REM sleep period that can last about an hour. NREM sleep lasts approximately 50% of this 90-minute sleep cycle in infants and about 80% in adults. As people age, in addition to less REM sleep, they tend to awaken at the transition from NREM to REM sleep.

APPROACH TO THE PATIENT

A thorough history and physical examination are indicated in the patient presenting with insomnia. Though insomnia can have many causes, it is closely associated with stress and depression. *(See Table 1)* In fact, recent evidence has established that an underlying mechanism in both disorders is hypothalamic-pituitary-adrenal (HPA) axis over reactivity resulting in excess secretion of corticotropin releasing factor (CRF), adrenocorticotropin releasing hormone, and cortisol.[1] Elevations in cortisol and CRF are directly related to poor sleep efficiency (the time required to go to sleep as well as the time spent in deeper levels of sleep).

Since over reactivity of the HPA axis is often a key factor in insomnia, it is important to utilize the techniques and natural approaches to stress management given in the Stress Management Clinical Highlight.

Another critical factor leading to impaired sleep quality is obesity and glycemic instability, especially in sleep-maintenance insomnia. Increased blood sugar volatility is a very important cause of sleep-maintenance insomnia, and poor sleep quality also carries with it an increased risk for developing Type 2 diabetes, as loss of deep-wave sleep impairs the ability to regulate blood sugar levels.[2] Likewise, the effects of stress, and, presumably, poor sleep quality, have now been linked as a significant risk factor in the development of obesity as well.[3] *(See Figure 2)*

The brain is highly dependent on glucose as an energy substrate, and a sudden drop in blood glucose level promotes awakening via the release of glucose regulatory hormones (i.e., epinephrine, glucagon, cortisol, and growth hormone). For this reason, one of the fundamental approaches to a patient with sleep maintenance insomnia is improving insulin sensitivity and reducing glycemic volatility. Please see the Clinical Highlight on Insulin Resistance for more information.

Lastly, a detailed accounting of prescription and nonprescription drug use history along with a dietary and beverage history is also required to determine whether the patient is consuming any stimulants or other agents known to interfere with sleep.

Focusing on these three areas (HPA over reactivity, obesity and glycemic volatility, and elimination of compounds that interfere with sleep) will help the majority of people with sleep disorders improve their sleep quality. For those requiring additional support, the use of natural compounds that promote improved sleep quality should be the first line of therapy versus the use of sedative hypnotic drugs.

5-HYDROXYTRYPTOPHAN (5-HTP)

Serotonin is an important initiator of sleep. The synthesis of central nervous system (CNS) serotonin depends on the availability of tryptophan. L-Tryptophan has shown modest effects in the treatment of sleep-onset insomnia, but dosages lower than 2,000 mg are generally ineffective. 5-HTP is one step closer to serotonin than L-tryptophan and does not depend on a transport system for entry into the brain. 5-HTP appears to produce better results than L-tryptophan in promoting and

Sleep-onset insomnia	Sleep-maintenance insomnia
Stress (HPA activation)	Stress (HPA activation)
Anxiety or tension	Depression
Environmental change	Glycemic instability
Emotional arousal	Sleep apnea
Fear of insomnia	Nocturnal myoclonus
Phobia of sleep	Environmental change
Disruptive environment	Parasomnias
Pain or discomfort	Pain or discomfort
Caffeine	Drugs
Alcohol	Alcohol

The boundary between the categories is not entirely distinct.

Table 1* **Causes of insomnia.**

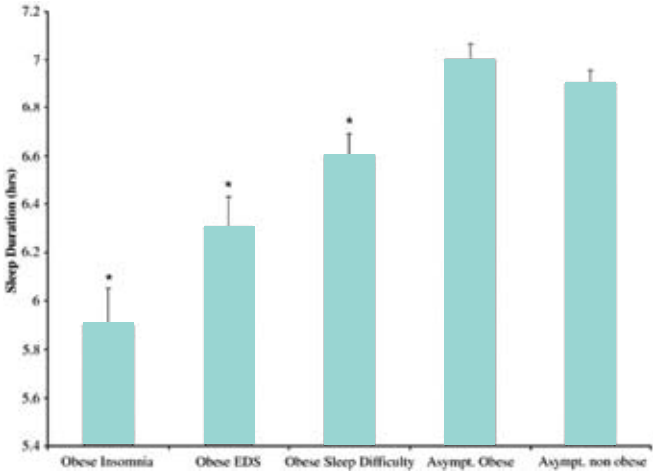

Figure 2 **Average sleep duration in obese individuals with sleep disturbance vs obese and nonobese individuals without subjective sleep disturbance (asymptomatic).** Data represent mean values +1 s.e. *P < 0.05 between obese individuals with sleep disturbance vs obese and nonobese individuals without sleep disturbance. EDS, excessive daytime sleepiness.

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maintaining sleep.[4, 5, 6] One of the key benefits of 5-HTP is its ability to increase REM sleep (typically by about 25%) while increasing deep sleep stages 3 and 4 without lengthening total sleep time. The sleep stages that are reduced to compensate for the increases are NREM stages 1 and 2—the least important stages. The dosage recommendation to take advantage of the sleep-promoting effects of 5-HTP is 50 to 300 mg, 30 to 45 minutes before retiring. Have the patient start with the lower dose for at least three days before increasing it.

MELATONIN

Several studies have shown that supplementation with melatonin is very effective in helping to induce and maintain sleep in children and adults. Melatonin also helps both people with normal sleep patterns and those with insomnia, while also helping to restore circadian rhythm.[7] (*See Figure 3)* However, the sleep-promoting effects of melatonin are most apparent only if melatonin levels are low. Melatonin appears to be most effective in treating insomnia in the elderly, in whom low melatonin levels are quite common.[8] A dose of 3 mg at bedtime is more than enough, because doses as low as 0.1 and 0.3 mg have been shown to produce a sedative effect when melatonin levels are low.

Somno-Pro™ provides 3 mg of melatonin along with 50 mg of 5-HTP and 200 mg of L-theanine per recommended dosage. L-theanine is a unique amino acid found almost exclusively in tea plants *(Camellia sinensis)*. In fact, L-theanine is the primary amino acid component of green tea comprising between 1 to 2% of the dry weight of tea leaves. Clinical studies have demonstrated that L-theanine reduces stress, improves the quality of sleep, diminishes the symptoms of the premenstrual syndrome, heightens mental acuity and reduces the negative side effects of caffeine.[9, 10] These clinical effects are directly related to L-theanine's ability to lessen sympathetic nervous system activity. Based on the results of clinical studies, it has been established that L-theanine is effective in the range of 50-200 mg.

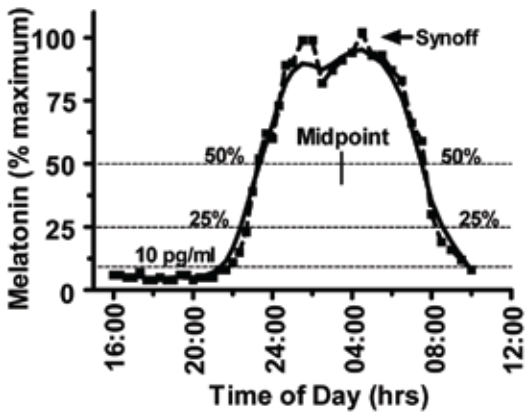

Figure 3 **Overnight plasma melatonin profile**. Plotted as a percentage of maximum (dashed line) and smoothed with a Lowess curve fit to the raw data (solid line). Some frequently used phase markers are shown: DLMO at 10 pg/ml, DLMO or dim-light melatonin offset (DLMOff) at 25% or 50% of maximum levels, the midpoint, and the termination of melatonin synthesis (Synoff).

The components of Somno-Pro™ appear to work synergistically to produce results that are better than those achieved with any of the ingredients taken individually.

MELATONIN AND METHYLCOBALAMIN IN SLEEP/WAKE DISORDERS

The exact function of melatonin is still poorly understood, but it is critically involved in the synchronization of hormone secretion and controlling sleep/wake cycles. Supplemental melatonin can produce sleep promotion as well as shifting the phase of the human circadian clock (sleep, endogenous melatonin, core body temperature, cortisol) to earlier (advance phase shift) or later (delay phase shift) times. The shifts induced are sufficient to synchronise to 24-hours most blind subjects suffering from non-24-hour sleep-wake disorder, with consequent benefits for sleep. Successful use of melatonin's chronobiotic properties has been reported in other sleep disorders associated with abnormal timing of the circadian system: jetlag, shiftwork, delayed sleep phase syndrome, and some sleep problems of the elderly.[11]

It is often useful to measure salivary melatonin levels at noon and at bedtime. Low nighttime melatonin levels may contribute to insomnia, sleep/wake disorders, disturbed mood, and other health disorders while high daytime melatonin levels are indicative of daytime sleepiness and sleep/wake disorders. Here are five basic patterns of melatonin secretion along with recommendations.

– Normal: no additional action is needed to restore proper melatonin secretion.
– Low nighttime, high daytime: this pattern represents what is referred to as a "sleep-wake disturbance." If a patient has this pattern, they will more than likely experience difficulty sleeping at night (perhaps even insomnia), along with excessive daytime sleepiness. Here are the key recommendations:

- Be aware that certain drugs can lead to this pattern, most notably caffeine, alcohol, tobacco, non-steroidal anti-inflammatory drugs (NSAIDs), like aspirin and ibuprofen; anti-anxiety and sedative-hypnotic drugs, like Lunesta, Valium and Halcion; antidepressant drugs, like Prozac, Zoloft, and Paxil; high blood pressure medicines (beta-blockers, adrenergics, and calcium channel blockers), and steroids, like prednisone. If possible, avoid use of melatonin-lowering substances at night
- Increase morning exposure to bright light in order to lower daytime melatonin production, and decrease evening exposure to bright light in order to increase nighttime melatonin production
- Evening supplementation with melatonin (usually 3 mg 45 minutes before retiring) will often help improve sleep quality, but will often create morning sleepiness. If this situation occurs, taking 1.5-3 mg of methylcobala-

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min (the active form of vitamin B12) orally the first thing in the morning can reset proper melatonin secretion, improve mental function, and eliminate daytime sleepiness (discussed in more detail below).
- If the patient exercises in the evening, have them switch to the morning, for evening exercise can decrease melatonin levels up to three hours after the end of exercise.
- To reduce daytime melatonin levels, avoid melatonin-containing foods, such as oats, corn, rice, ginger, tomatoes, bananas, and barley. It is also a good idea to avoid foods high in tryptophan (melatonin precursor), such as milk and all dairy products, chicken liver, pumpkin seeds, turkey, chicken, watermelon seeds, almonds, peanuts, and brewer's yeast. Conversely, these same foods can be used to increase nighttime melatonin production.
- Do not use electric blankets. Electromagnetic radiation can suppress melatonin secretion.

– Low nighttime, normal or low daytime: the patient likely suffers from insomnia with these patterns. Follow all of the recommendations given above and have them avoid exposure to bright light at night. Even exposure to bright light for more than just a few minutes rapidly reduces melatonin production.
– High nighttime, high daytime: this pattern is usually the result of taking too much melatonin or significant hormonal disturbances. These sorts of disturbances are more obvious in women and may include menstrual abnormalities or even infertility. Taking 1.5-3 mg of methylcobalamin orally the first thing in the morning may help reset proper melatonin secretion.
– High nighttime, normal or low daytime: this pattern is usually the result of taking too much melatonin. Otherwise, it is important to increase your daily exposure to sunlight or bright light.

METHYLCOBALAMIN

The active form of vitamin B12, methylcobalamin, is useful in both high and low melatonin secretion as it plays a major role in normal melatonin secretion.[12] Low levels of melatonin (especially in the elderly) may be a result of low vitamin B12 status. Vitamin B12 is available in several forms. The most common form is cyanocobalamin; however, vitamin B12 is most active in the form of methylcobalamin. While methylcobalamin is active immediately upon absorption, cyanocobalamin must be converted to methylcobalamin by the body removing the cyanide molecule (the amount of cyanide produced in this process is extremely small) and adding a methyl group. Cyanocobalamin is not as effective as methylcobalamin in improving melatonin secretion.

Several studies have shown that methylcobalamin (dosage 1.5 to 3 mg) is an effective treatment of sleep-wake disorders (shift workers, excessive daytime sleepiness, restless nights, and frequent nighttime awakenings) that are attributed to abnormal melatonin secretion.[13, 14] Subjects taking methylcobalamin experience improved sleep quality, increased daytime alertness and concentration, and, in some cases, improved mood. Much of the benefit appears to be a result of methylcobalamin influencing melatonin secretion. However, benefits may also be a result of unmasking low brain levels of methylcobalamin. A low level of methylcobalamin is one of the most common nutrient deficiencies, especially in the elderly. The low levels of melatonin in the elderly may be a result of low vitamin B12 status.

Utilizing methylcobalamin in the morning and melatonin at bedtime appears to be a suitable recommendation for sleep/wake disturbances.

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FIGURES

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TABLES

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