



## What is Sleep?

In humans, "normal" sleep varies by individual, cultural, and historical practice (e.g., siestas). However, the normal sleep pattern for an American first-shift (daytime) worker (or student) starts in the late evening, and includes four stages of non-rapid eye movement (NREM) sleep, interwoven with shorter periods of REM sleep (associated with dreaming) that increase in length as night progresses to morning.

Normal diurnal humans spend 75-80% of our sleep time in the four stages of NREM, with little dreaming and a relatively quiet brain. Stages N3 and N4, also called "delta-wave" sleep, are the deepest sleep periods; delta sleep rebounds after deprivation, as does REM sleep. Normally, increasing periods of REM sleep follow delta sleep, followed by returns to N1 or N2 during which the sleeper is most likely to remember the preceding REM dream.

### Normal sleep architecture

Stage	Description	Duration	EEG Brainwave pattern	Events and abnormalities
W	Wakefulness	~16 hours	Alpha waves	Daytime consciousness
N1	Somnolence; "drowsy", easily awakened	1-5%	Theta waves	Hypnagogic twitches, hallucinations
N2	Asleep	<50%	Slower waves, sleep spindles, K-complexes	Unconsciousness
N3 (SWS)	Slow Wave Sleep Transition to deep sleep	~7%	< 50% delta waves	Melatonin peak, night terrors, parasomnias
N4 (SWS)	Slow Wave Sleep Deep sleep	~20-25%	>50% delta waves	Minimum core temperature, rebounds after deprivation
REM 1-4	Rapid Eye Movement	~20-25%	Rapid low-voltage EEG	Dreaming, low muscle tone, rebounds after deprivation

Adults spend about 90-120 minutes per night in REM sleep in 4-5 periods that lengthen through the night. Newborns spend more than 80% of their sleep time in REM, while adults only 20-25%. While the elderly generally sleep fewer total hours and spend less time in delta sleep, it is not clear whether this is a normal pattern of aging or a side effect of accumulated ills associated with aging.

For diagnostic and treatment purposes, "normal sleep architecture" can be defined as getting sufficient REM and delta-wave sleep within a normal range of total sleep time (around 7-9 hours/night or a "full night's sleep") to feel refreshed in the morning after a "good night's sleep".

## Insomnia

Inadequate or non-restorative sleep, difficulty falling asleep or, once asleep, staying asleep, characterizes insomnia. Feeling drowsy, unrested or functionally impaired during waking hours is typical. Insomnia can be transient or mild (little wake-time impairment), short-term or moderate (impaired wake time for less than a month), chronic or severe (tired and irritable when awake, restless and anxious when trying to sleep which lasts more than a month).

Insomnia is exacerbated by circadian disruptions such as artificial light, imposed school and work schedules, background noise, television, etc. Additional external influences include travel across time zones, poor sleep hygiene, personal stress, pain, co-morbid mood disorders, and the widespread use of caffeine, alcohol, medications and other drugs.

Insomnia increases with age and is more common in females, although reasons are unclear. Insomnia is a co-morbidity of depression and anxiety disorders, and life stress is a common cause of acute insomnia. Insomnia may accompany other sleep disorders (e.g., apnea, bruxism, restless legs syndrome), yet many patients experience primary insomnia with no obvious cause.

With aging populations, insomnia is a growing medical problem. The most significant public health risks of sleep deprivation are accidents on the road, on the job and, especially for the elderly, in the home. Poor sleep is associated with higher rates of illness and absenteeism as well as poor job performance. Inadequate sleep is also associated with weight gain, diabetes and heart disease. Prevention of these conditions should thus fuel the demand for better insomnia treatments.

## Insomnia Treatments

Approaches to treating insomnia vary widely: acupuncture, aromatherapy, cognitive behavior therapy, herbal remedies, sleep hygiene, relaxation techniques, OTC drugs (mostly antihistamines) and prescription pharmaceuticals.

Prescription therapies approved for insomnia may be divided into four drug classes:

Barbiturates (once very popular, but largely supplanted by the newer drugs),

Benzodiazepine sedatives (still the most used category of sleep drugs),

Non-benzodiazepine "Z-drugs", with faster onset of action and shorter half-lives than the benzodiazepines (the fastest growing drug class, including the three top-selling insomnia drugs).

Sedating antidepressants are widely used for insomnia associated with mood disorders, but also used off-label for insomnia in the absence of a mood diagnosis.

Many drugs are in clinical development with several in the non-benzodiazepine GABA agonist class, plus a few novel agents active at receptors for the pineal gland hormones melatonin and orexin (sleep/wake-specific targets). Also in development are Histamine H1 antagonists and sedating antidepressants that are being clinically tested specifically for insomnia.

## Insomnia Market Opportunity

Although insomnia is the most highly prevalent (~10-50% of population, depending on how defined and in which country) sleep disorder, only a fraction of patients pursue pharmaceutical treatments. Worldwide, the prescription insomnia therapeutics market is estimated at \$3.3 billion. In the United States, approximately 70 million prescriptions are written annually for insomnia, representing a \$1.8 billion market, with a 5-10% annual growth rate. However, of the 40-70 million American adults who suffer insomnia (of which 25 million are chronic or severe cases), only 20% take prescription sleep aids.

The ideal therapeutic would quickly induce sleep, maintain normal sleep architecture and allow timely awakening without hangover and with improved daytime function. However, many patients and physicians avoid drugs because of perceived risks of inefficacy, dependence, hangover, rebound insomnia, safety concerns and other side effects (memory impairment, confusion, sedation).

Chronic insomniacs are particularly in need of improved therapeutics that allow long-term use without fear of dependence or hangover. Additionally, people who are shift-workers and frequent time-zone travelers may benefit from an improved therapeutic.

## The Somnus Approach

Somnus sees a significant opportunity for new treatments in this underpenetrated multi-billion dollar prescription market. Although there are many drugs on the market and in development for short-term insomnia, Somnus is aiming for a less crowded target indication: the unmet need for sleep maintenance. Taking advantage of advances in clinical sleep testing as well as in controlled-release formulation and technology, Somnus is developing a product that more closely approaches the ideal sleep therapeutic.

SKP-1041 is a non-benzodiazepine hypnotic agent in-licensed from Skye Pharma. Delivery using Skye's patented GeoClock controlled-release technology will enable users taking a single oral dose at the beginning of their sleep cycle to obtain a full period of sleep with a more natural sleep architecture.

Somnus is already pursuing clinical studies in Europe and plans to start additional clinical studies in the United States later in 2008.