

Insomnia

What is insomnia?

Insomnia is a sleep disorder. The word is derived from the Latin noun "somnia", meaning dream. People with insomnia: (i) have difficulty falling asleep; (ii) often wake up during the night and have problems going back to sleep; (iii) wake up too early in the morning; and (iv) experience unrefreshing sleep. Insomniacs may suffer from one or more of these problems. Insomnia can cause problems during the day, such as sleepiness, fatigue, difficulty in concentrating, and irritability. The disorder is not defined by the number of hours someone sleeps every night, as the amount of sleep a person needs varies. While most people get along with seven or eight hours of sleep, some people do well with less, and others may need more. Most people who sleep poorly at night remain in bed for too long and this increases the time spent lying awake. Many insomniacs have intrusive thoughts before falling asleep or if they wake during the night and preoccupation with these causes difficulty with maintaining sleep.

There is primary or secondary insomnia. **Primary insomnia** is characterised by sleep problems that are not directly associated with any other issue. **Secondary insomnia** means that a person is having sleep problems because of a health condition such as depression, heartburn, asthma, and general pain or conditions caused by medication. Sleeplessness can be acute or short-term, while chronic insomnia has a longer history. **Acute insomnia** lasts from one night to a few weeks. It is often caused by emotional discomfort and can be related to a single specific event. **Chronic insomnia** is when a person suffers from sleeplessness at least three nights a week for one month or longer. It can have many causes and often occurs along with other health problems.

An evaluation to establish the diagnosis of insomnia may include a physical examination, taking a medical history, and a sleep history. People are often asked to keep a sleep diary for some weeks. In some cases, patients may be referred to a sleep centre for special tests.

Insomnia is a common disorder, where the patient has difficulty in sleeping. It has many causes and can make lives miserable. Many medicines have been developed, but new approaches are still needed.



Behaviours and insomnia

Behaviours have been shown to perpetuate insomnia in some people:

- expecting to have difficulty sleeping and worrying about it
- ingesting excessive amounts of caffeine
- drinking alcohol before bedtime
- smoking cigarettes before bedtime
- excessive napping in the afternoon or evening
- irregular or continually disrupted sleep/wake schedules

Who does insomnia affect?

In 1999, a survey conducted in four European countries (France, Germany, Great Britain and Spain) through interviews with approximately 2,000 adult people in each country, revealed a mean prevalence of insomnia ranging from 30 to 45 per cent, in accordance with previous studies. This means that some 100 million people suffer from some sort of insomnia in the EU. Another interesting revelation of this study was that 60 per cent of the insomniacs interviewed declared that they did not suffer from sleeping problems every night, confirming the fluctuating nature of this disorder. Insomnia tends to increase with age and affects about 40 per cent of women and 30 per cent of men.

In the USA, some 70 million people suffer from sleep disorders. A National Sleep Foundation survey, carried out in 2002, revealed that 35 per cent of the adult USA population said they had experienced insomnia every night or most nights for the past year.

Present treatments

A short-term episode of insomnia may be treated with herbal excipients or may not require treatment at all. But if insomnia makes it hard for people to function during the day because of tiredness, medication is needed for a limited time. Treatment for chronic insomnia includes first treating any underlying health problems that are causing the sleeplessness. If insomnia continues, behavioural therapy and medication are suggested. Current treatments include benzodiazepine receptor agonists, gamma-aminobutyric acid (GABA) receptor agonists and dual-acting treatments that agonise both benzodiazepine and GABA receptors.

Whichever medicine is used should only be prescribed nightly for three weeks and then on alternate nights for another three weeks or on an intermittent basis, so that the patient has some control over the quality of sleep obtained, but does not develop dependency. Short-term hypnotic treatment complements the non-pharmacological techniques, such as keeping a sleep diary, applying relaxation techniques, developing realistic sleep expectations and enhancing the patient's ability to cope with the stresses which contribute to insomnia.

What's in the development pipeline?

In September 2004, an approval application for a new class of sleep disorder medicines was submitted to the authorities. The molecule in question is a selective melatonin 1 agonist. Apparently, it is the first insomnia treatment to be developed in 35 years. Melatonin 1 and its partner melatonin 2 have receptors in the brain's suprachiasmatic nuclei - the area above the crossing of the ophthalmic nerves which is responsible for regulating the 24-hour sleep-wake cycle. Melatonin 1 regulates sleepiness while melatonin 2 is responsible for helping the body shift between phases of night and day.

Other melatonin agonists are under investigation. One product, for the treatment of insomnia in the elderly, has reached the submission stage, while two more compounds are both in clinical phase 2.

There are further clinical investigations phase 2 with melatonin 1 agonists to treat circadian rhythm sleep disorder.

Modified- and immediate-release formulations of a GABA A receptor agonist for the treatment of insomnia were filed. Modified release (MR) forms have been developed for use in elderly patients with sleep maintenance difficulties. Patients on the new MR therapy had increased total sleep time, and also reported greater improvements in sleep maintenance endpoints: wake after sleep onset, total wake time and number of awakenings after sleep onset. Patients on the medicine also found it easier to get to

sleep - with latency to sleep onset being significantly improved.

Clinical investigations phase 3 with a slow release form of a compound acting as an omega benzodiazepine agonist are also underway.

Other research groups are running an ambitious phase 3 programme for a GABA receptor agonist which is being evaluated for insomnia in patients suffering from depression, those with rheumatoid arthritis, and in women with perimenopausal symptoms. A muscimol analogue with GABA A receptor agonist activity is in phase 3 trials, with an approval expected in mid 2007.



The longer-term future

Most surveys dealing with insomnia have shown that there was a suboptimal use of medical resources by the majority of insomniacs. This highlights the urgency of developing new approaches to the use of sleeping medications capable of reconciling public health constraints with provision of an optimal service to the patient. The primary goals are to prevent psychological dependence on hypnotics and to rationalise their usage on an "as needed" basis.

Recently, researchers have located two centres, which they believe constitute the "sleep switch" in the human brain. An area in the front of the hypothalamus, the ventrolateral preoptic nucleus contains neurons that are active during sleep, while the posterior lateral hypothalamus contains neurons that are crucial for maintaining normal wakefulness. Taken together, these interdependent structures are considered to be a "sleep switch" that keeps people awake during daytime and asleep through the night. The hope with these findings is that new medicines, rather than sedating the entire central nervous system, might act specifically on the centres that actually control sleep, providing something closer to natural sleep.

Neuropeptides are another focus of ongoing research. The neuropeptide hypocretin, also known as orexin, has been implicated in waking, since its deletion leads to the sleep disorder narcolepsy. Animal models have revealed that damaging hypocretin receptor bearing neurons located in the brain area known as *substantia nigra* produces insomnia. Research is ongoing to find out whether insomnia following lesions of the *substantia nigra* is a direct effect or whether sleeplessness is secondary to increased motor activity resulting from reduction of tonic inhibitory control by the *substantia nigra*.

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