

NARCOLEPSY: A TREATMENT FOR INSOMNIA?

by Steven Grenard RRT, RPSGT



Narcolepsy is well known to sleep specialists and technologists as a condition that affects at least 1 out of 2000 Americans. The disorder is marked by relentless pathologic sleepiness when the victim should be alert after an apparently good night's sleep plus a condition called cataplexy involving weakness and collapse as part of an otherwise normal emotional response including laughter. "Please don't make me laugh" is a common plea voiced by people with narcolepsy with cataplexy although not all narcolepsy patients have cataplexy.

In addition people with narcolepsy often report hallucinations and sleep paralysis. These symptoms, along with cataplexy, are often reported to doctors by patients and are clues to the likelihood that narcolepsy is involved. The condition is commonly diagnosed by an all night polysomnograph followed the next day by a sojourn in the lab to undergo a series of four, possibly five 20-minute nap trials in a procedure called the Multiple Sleep Latency Test or MSLT for short. If the subject demonstrates REM sleep in 20 minutes or less on at least 2 naps the diagnosis is generally positive for narcolepsy. The fifth nap is scheduled if a patient had one sleep onset REM period (SOREMP) amongst the first four trials.

The underlying cause of narcolepsy is a deficiency in two hormones known as orexins 1 and 2 which are produced and liberated by specific neurons in the hypothalamus. These neuropeptide hormones find their

way into cerebrospinal fluid that bathes the brain and spinal cord as well as regions of the brain that function in the regulation of wakefulness and other circadian aspects of the wake/sleep cycle. Orexin is a name coined by Masashi Yanagisawa and colleagues at the Univ of Texas SW Medical Center in Dallas. Their use of the term was to reflect the "orexigenic" or probable appetite stimulating activity of these substances. Independently another group of researchers led by Luis DeLecea and Thomas Kilduff discovered these same peptides but called them hypocretins because they were similar to incretins and were produced by neurons in the hypothalamus. Both terms have come under criticism for a variety of reasons and some nit pickers have suggested a compromise name: hyporexin. We'll stick with orexins for now.

Treatment of narcolepsy has been principally to relieve the symptoms of sleepiness with stimulants such as methylphenidate and amphetamines and a newer class of drug, modafinil which is safer and has neither of the side effects of the earlier drugs. But now researchers are developing drugs which affect either the orexin/hypocretin receptors or the production of these substances directly. Pharmaceutical researchers are also capitalizing on the fact that people with insomnia can be helped to sleep normally by taking drugs which cause a decrease in orexins (orexin antagonists or inhibitors) or the effect of orexins (orexin receptor antagonists). Narcolepsy causes sleepiness, insomnia wakefulness. Orexin deficiency causes narcolepsy so the reasoning is that an orexin deficit, induced by orexin antagonists, will diminish wakefulness and promote sleepiness. A group of Swiss Researchers (Brisbare-Roche et al) writing in the February 2007 issue of Nature Medicine reported that they were able to induce sleepiness in rats, dogs and human test subjects by pharmacologically blocking both orexin 1 and orexin 2 receptors. When their Orexin 1 & 2 antagonist is administered during the active period of the circadian cycle, they were able to increase the duration of both REM and non-REM sleep in lab rats in contrast to sleeping medications modulating GABA(A) receptors.

In dogs sleepiness occurred and increased "surrogate markers" of REM sleep were increased. And in humans it resulted in both subjective and objective (polysomnographic) signs of sleep including shortened latency to Stage 2 sleep and decreased alertness, both objectives of the trial. But the best part of these observations is that while cataplexy is a common and unpleasant, even a risky marker of narcolepsy, there was no sign of the problem observed in test subjects who were helped to sleep by inducing an orexin deficit. Needless to say any drug designed to promote sleepiness should be taken at bedtime.

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Other recent research indicates that the orexin system may have a major role integrating metabolic, circadian and sleep debt influences in determining whether people and other mammals should be asleep or awake, alert and active. Experiments involving central administration of orexin 1 strongly promoted wakefulness, increased body temperature and provoked an increase in energy expenditure. What's more, orexin 1 seems to be increased by sleep deprivation. Some researchers feel that the orexin/hypocretin system may be even more important in the regulation of energy expenditure than food. And according to some researchers, individuals with narcolepsy, who are deficient in orexins, have increased obesity rather than the reverse (decreased BMI) than if orexin was primarily just an appetite stimulator.

While this research is starting to warm up, the use of orexin inhibitors has been postulated for years for the treatment of addictions and overeating. Expect also to see a possible role for orexin blockers in the treatment of alcoholism. Alcoholic lab rats given drugs targeting the orexin system lost interest in imbibing alcohol even though it was freely available to them and readily consumed before the orexin antagonists were administered.

The February, 2007 issue of the Pharmaceutical Journal Online published the following item:

"An antagonist of the orexin OX1/OX2 receptor — ACT-078573 — being developed by Actelion may prove useful for people suffering from sleep disorders. The company reports that a study involving 39 patients with primary insomnia indicates that the compound improves sleep efficiency as measured by polysomnography. The study follows research published in Nature Medicine this month that shows an increase in sleep in animals and healthy volunteers (2007;13:150). Actelion says that ACT-078573 is the first oral orexin receptor antagonist that penetrates the blood-brain barrier and is capable of inducing transient and reversible blockade of the OX1 and OX2 receptors." Actelion is a Swiss based company.

And at the JP Morgan Healthcare Conference held January 10, 2007 in San Francisco Human Genome Sciences of Maryland issued the following as part of a press release regarding an orexin antagonist being developed by GlaxoSmithKline (GSK) in which it has an interest:


"In the third quarter of 2006, GSK initiated clinical development of GSK 649868, an orexin antagonist, for the treatment of sleep disorders. These small-molecule drugs, as well as darapladib for atherosclerosis and relacatib for bone disease, were discovered by GSK based on HGS technology."

Turning the undesirable symptom(s) of one disease, in this case sleepiness in narcolepsy, into a weapon to fight another problem, wakefulness in insomnia, is an example of what one phase of modern pharmacological research can achieve.




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shift you would normally go home and sleep from 0900 to 1500, then on your day off, try to take a nap sometime during this period. This will help to minimize the disruption to your circadian rhythm caused by working nights.

It also turns out that my old 20 minute napping practice way back when in the NICU was a pretty good idea. Short naps have been shown to improve function and measurably reduce sleepiness among night shift workers. I heartily recommend a short nap as a very civilized thing for folks to do. If employees want to use their meal and break times to nap on night shift, I think hospitals ought to be very tolerant of this. In fact, maybe hospitals ought to rethink the whole way we staff night shift. As the science of sleep disruption grows, and as our ability to carefully measure the quality of clinical care improves, it may be that we find a strong link between night shift related sleep disruption and poor quality clinical care. If this turns out to be true then maybe we ought to rethink long night shifts. Perhaps sleeping rooms should be built and night shift staff should have the option or even be required to sleep two hours for every four or six hours worked on night shift.

No one yet knows the scope and magnitude of this issue, but I suspect the way we staff and managing hospitals after hours will change very much in the next 20-30 years.

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