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Innovations

In the Arms of Morpheus: Actelion Keeps Sleepers from Waking

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Your sleep cycles ebb and flow, governed by hormones and light, just as tides are pulled by the moon. But the artificial rhythms of our society, including shift work and air travel across time zones, are not conducive to rest. A third of Americans suffer from sleeplessness, according to the NIH. Because screening and diagnosis is not uniform, prevalence is uncertain. At least 30 million Americans are estimated to experience insomnia, but the number could be much higher. It is unclear how many are chronic insomniacs.

There are dozens of sleep disorders, but insomnia, sleep apnea, and circadian rhythm disorders are the most common.

As sleep is governed by hormones, lack of sleep or poor quality sleep is increasingly correlated to heart disease, diabetes and obesity.

Most insomnia is transitory, caused by stress. Sleep disturbance can also be triggered by alcohol, caffeine, cigarette smoking, and certain prescription drugs. Most commonly, insomnia is comorbid with other conditions such as depression, anxiety, ADHD in children, dementia, and various physical problems, including diabetes (NIH State-of-the-Science Statement on Manifestations and Management of Chronic Insomnia in Adults, http://consensus.nih.gov/2005/2005InsomniaSOS026html.htm).

According to Joyce Walsleben, Ph.D., associate professor of medicine at the NYU Langone Medical Center, insomnia is commonly treated by drugs and behavioral therapies. People experiencing transient insomnia will try to self-medicate with alcohol or antihistamines or will mention it to a general practitioner, who, strapped for time, will prescribe a sleep drug. If they go to a sleep specialist, it is typically to get off the medication. They will probably be offered a mixed course of drugs, short-term, and then behavioral therapy.

New drugs in development like Actelion's Almorexant are not intended to put you to sleep, but rather to keep you from waking and to prevent grogginess. They are targeted at a potentially large market. Windhover Information, Inc., values the worldwide insomnia market as worth $4.6 billion: $3.5 billion in the U.S., $700 million in Europe, and $460 million in Japan.

Valley of the Dolls

Readers of a certain vintage may recall "Valley of the Dolls," Jacqueline Susann's 1966 bestseller about starlets, sex, and drugs. "Dolls" were tranquilizers. Satirically immortalized in "Mother's Little Helper" by the Rolling Stones, benzodiazepine receptor agonists were prescribed for stress in the 1960s and 1970s. These sedatives enhanced the effects of gamma-aminobutyric acid (GABA) an inhibitory neurotransmitter in the central nervous system. However, they led to cognitive problems and addiction.

Several next-generation sedative-hypnotics, called nonbenzodiazepines, informally known as "Z" drugs, include zolpidem, now generic (marketed as Ambien by Sanofi Aventis); zolpidem CR; zaleplon, now generic (marketed as Sonata by King Pharmaceuticals); and eszopliclone (Sepracor's Lunesta, the only drug of this category approved for long-term use). As they selectively bind to the $GABA_A$ receptor, they produce fewer side effects but still can cause dependence. In 2007, the FDA instituted stronger labeling for these sedative-hypnotics, as people who took them occasionally experienced anaphylaxis and swelling as well as made phone calls, raided the refrigerator, and drove while asleep with no memory of doing so.

Takeda Pharmaceuticals' Ramelteon (marketed as Rozerem) melatonin receptor agonist, which targets receptors that regulate the circadian sleep-wake cycle, is approved by the FDA for long-term use. Ramelteon selectively binds to the MT_1 and MT_2 receptors in the suprachiasmatic nucleus (SCN) instead of $GABA_A$ receptors, as do the Z drugs, hopefully bypassing side effects.

Other medications, such as antidepressants and antipsychotics, are prescribed off-label for insomnia. Over- the-counter drugs include antihistamines, melatonin, valerian, and L-tryptophan, all which have uncertain effectiveness.

Terra Incognita inside Your Head

Researchers can monitor the successive phases of rapid eye movement (REM), when dreaming and memory consolidation is believed to take place, and the four stages of non-REM sleep (NREM). But nobody really knows why we sleep. Sleep seems to restore body and mind, consolidate memories, and reinforce learning. It may nurture brain plasticity. The need for sleep varies between individuals. Humans sleep between 7 and 9 hr in a 24 hr cycle. Sleep patterns and quality change throughout one's lifetime. Unfortunately, quality of sleep is hard to measure.

While insomnia is synonymous with misery and in the short-term can impair mental function and memory, its long-term effects are unclear. In one experiment, rats deprived of sleep died within weeks. But unlike rats, people don't die of sleeplessness, except for a few who suffer from a rare genetic condition called fatal familial sleep disorder.

"I think the more pressing question is that the drugs have side effects," said Dr. Jerome Siegel, director of the Sleep Research Center at UCLA. "I am not aware of any evidence that sleeping pills have a health benefit." According to

Siegel, the lingering effects of drugs can affect daytime function.

Studies show that fatigue from sleep deprivation in shift work can lead to mistakes and accidents, as well. Shift workers also can experience greater rates of irritability and depression and report increased gastrointestinal and cardiovascular disorders. (Scott, 2000).

Siegel refers to a study of over 1.1 million subjects commissioned by the American Cancer Society (Kripke et al., 2002) which showed that chronic users of hypnotics had shortened lifespans, whereas people with untreated insomnia didn't. However, sleep time was not directly related to lifespan. More than one epidemiological study shows that across a population, sleepers are on a U-shaped curve. People who get too much sleep or people lacking sleep tend to die quicker, but, Siegel says, those with increased sleep are actually at greater risk than those with decreased sleep.

As sleep is governed by hormones, lack of sleep or poor quality sleep is increasingly correlated to heart disease, diabetes, and obesity. Professor Eve Van Cauter, at the Department of Medicine at the University of Chicago, managed to turn a group of young people into the equivalent of diabetics by depriving them of sleep for a week (Knutson and Van Cauter, 2008).

However, these studies on health effects were done on normal people, says James Walsh, Ph.D, director of the Sleep Medical Center, St Luke's Hospital, and scientific board member of Somnus Therapeutics, a sleep drug startup. Few studies have been done on insomniacs.

New Hope for Night Owls

Research into the brain's reward system paved the way for Swiss company Actelion's (http://www.actelion.com) compound Almorexant (ACT078573), an orexin receptor antagonist. Almorexant doesn't put you to sleep, but it keeps you from waking up prematurely.

Actelion, incorporated in 1997, is public. The company is also engaged in developing new chemical entities and compounds based on ion channels, aspartic proteinases, and GPCRs. Actelion is also in the enviable position of having a billion dollars of cash in the bank.

Orexins (or hypocretins) are neuropeptide modulators produced by the brain that direct wakefulness and reward seeking behavior. "The existing drugs induce your brain not to work, [causing] anesthesia." says Actelion's CEO, Jean-Paul Clozel. "They decrease the function of the brain. You use your night to make order in the brain. Orexin prevents you from waking up. If you wake up, you go back to sleep normally. You are dreaming normally."

In a collaboration with GlaxoSmithKline that started in 2008, Almorexant entered RESTORA 1 (REstore normal physiological Sleep with The Orexin Receptor antagonist Almorexant), a phase III study comparing it to Ambien. So far, according to Clozel, study subjects have not demonstrated clinical ill effects or next-day impairment in motor skills and reaction time.

Not Letting Sleeping Dogs Lie

The hypocretin/orexin peptides and receptors were discovered in 1998 by two groups independently: one led by Luis de Lecea, Ph.D., at Stanford, who called them hypocretins (HCRT) to show they are a hypothalamic member of the incretin family; and another, headed by Dr. Takeshi Sakurai at the University of Tsukuba, Japan, who named them orexins, as they help regulate feeding behavior.

"The first experiments were oriented towards obesity, but it was clear it wasn't the main function," said de Lecea. "The peptide functions in arousal, brain reward, and goal seeking behaviors." According to de Lecea, there are two different hypocretin receptors. The mutation in receptor 2 results in narcolepsy in dogs and has arousal functions. The functions of receptor 1 are still unknown. Human and canine narcolepsy is the same disease, resulting from a malfunction of HCRT, but narcolepsy is genetic in dogs and probably an immune malfunction in humans. Both receptors are widespread throughout the brain as well as in other tissues. "Obviously, the compound of Actelion is a nonselective inhibitor of both receptors," de Lecea said. "It might affect both arousal and behavior."

Second Acts for Old Drugs

In sleep drugs, dose matters. San Diego-based Somaxon (http://www.somaxon.com) is reformulating doxepin, a generic antidepressant and selective H1 antagonist, betting that in low doses it will not produce the side effects associated with higher doses of the drug. Dr. Neil Kavey, a psychiatrist at Columbia Presbyterian Medical Center, noticed his patients who took doxepin slept through the night, and prescribed it off-label for insomnia.

The company, founded in 2003, is public. Silenor, a low-dose (1–6 mg) formulation of doxepin for patients with chronic insomnia, is currently awaiting FDA approval. The company has conducted four randomized, placebo-controlled phase III trials on groups with transient and chronic insomnia, ranging from 229 to 565 people, to measure effects including sleep onset, sleep maintenance, early morning awakenings, and residual effects.

New Jersey startup Somnus (http://www.somnusthera.com) is taking advantage of zaleplon's short half-life, reformulating it for timed release. According to James Walsh, tinkering with the half-life of a generic drug with an established safety profile to turn it into a sleep maintenance drug is hypothetically attractive. The company is attempting to calibrate the drug to kick in after the first few hours of natural sleep, but as Walsh points out, there is variability in how people metabolize drugs. The rejiggered drug still is regarded as potentially addictive. Somnus' French scientific collaborator will shortly begin testing patients on driving simulators to check for residual effects on coordination.

But can the quick-fix these drugs promise be more effective than behavioral methods? A 6 week course in cognitive behavior therapy (CBT) achieves impressive results that are still evident 6 months out, but the effects of a pill cease when you stop taking it. According to Walsh, it is often a matter of patient and doctor preference, but skilled CBT practitioners are scarce, and while insurance companies may not pay for a psychologist, they will pay for drugs.

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