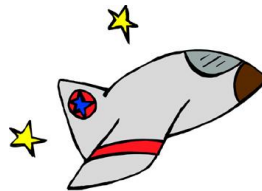




Small Doses.....

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Jet Lag - Current and Potential Therapies

Jet lag, also known as circadian desynchrony, is a sleep disorder where there is a mismatch with the body's natural circadian rhythm and the external environment, usually due to rapid travel across multiple time zones. This common problem affects all age groups, but may have more pronounced effects on the elderly whose recovery rate may be more prolonged than that in young adults.



A multitude of factors, such as the number of time zones crossed, the time of travel, and the direction traveled play a role in the severity of symptoms experienced by travelers. Travelers usually experience symptoms after crossing at least two time zones. Symptoms may include disturbed sleep, daytime fatigue, decreased ability to perform mental and physical tasks, reduced alertness, and headaches. Sleep disturbances typically last for a few days, but they can persist for as long as a week if the change in time is greater than eight hours. Eastbound travel is associated with a longer duration of jet lag than westbound travel.



Role of the Internal Circadian Clock

To appreciate the factors associated with jet lag, it is helpful to understand the basic properties of the body's internal clock. The central circadian clock is located in the hypothalamus, where light signals from the retina are received. It is responsible for adapting the circadian rhythm according to the light–dark cycles of the environment and for generating neuronal and hormonal activities that regulate various body functions in a 24-hour cycle.

Zeitgebers (time-givers or synchronizers) are rhythmic cues in the environment that synchronize the internal body clock to the earth's 24-hour light–dark cycle. Light is the strongest *zeitgeber*; other non-photic *zeitgebers* include temperature, social interaction, pharmacological manipulation, exercise, and meal timing. It is easiest to initiate sleep when the body temperature is at its lowest, coupled with an increase in melatonin secretion. When the body clock is inappropriately phased, sleep is difficult to initiate and maintain.

Prevention and Management of Jet Lag

The goal of prevention and treatment of jet lag is to achieve circadian realignment in the most rapid and efficient way possible while minimizing the symptoms. The aggressiveness of treatment often depends on the length of stay in the new time zone. For example, business travelers, pilots, and flight attendants may experience frequent but brief shifts in time zones, and it may be practical for them to just remain on their normal sleep/wake schedule.



Light Therapy

Sunlight has a major influence on the internal circadian clock. Traveling across several time zones necessitates resetting and adjusting to a new daylight schedule. Natural light exposure is the ideal mechanism for counteracting jet lag. For those who travel frequently or are unable to have exposure to natural sunlight, exposure to bright artificial light may be of benefit.

Melatonin

In the human body, sleep is initiated during a rise in the concentration of melatonin and during the declining phase of body temperature. Synthesized from serotonin in the pineal gland, melatonin helps shift human circadian rhythms. An increase in melatonin alerts the body that "biological night" is starting, whereas a decline in melatonin alerts the human body that biological night is ending. Administering exogenous melatonin in the afternoon to evening hours of a 24-hour day promotes an advance in circadian rhythm, which may help travelers overcome symptoms.

Ramelteon

Ramelteon (Rozerem®), a melatonin receptor agonist, has been approved by the FDA for insomnia. The dose is usually 8 mg, taken one half-hour before bedtime. The selectivity of ramelteon for melatonin receptors, normally acted upon by endogenous melatonin, induces sleep and can help maintain the circadian rhythm underlying the normal sleep-wake cycle. Adverse effects of ramelteon are similar to those of melatonin. It does not appear that ramelteon leads to dependence or withdrawal effects after discontinuation.

Zolpidem

Zolpidem (Ambien®), a non-benzodiazepine hypnotic, binds the benzodiazepine receptor subunit of the GABA-A receptor complex. It has a strong hypnotic effect, with weak anticonvulsant and muscle-relaxant properties. Although the FDA has not approved this drug for jet lag, the use of zolpidem as a way to cope with symptoms might be suitable for those who travel often for work and who are required to be active and alert as soon as they arrive in the new time zone. It is effective because of its rapid absorption, short half-life, and inactive metabolites. Adverse effects include dizziness, somnolence, memory loss, headache, and nausea. When low doses recommended for initiating sleep are used, carryover effects should be minimal the next day.



Caffeine

Caffeine is a common remedy for treating sleepiness induced by jet lag. Studies have shown that it can be an effective way to reduce or overcome symptoms of jet lag. One study found that caffeine led to an objective decrease in daytime sleepiness compared with melatonin and placebo, as assessed by multiple sleep latency tests.



Diphenhydramine

(Benadryl[®]) is the most common nonprescription antihistamine prescribed for insomnia. Side effects can include daytime sleepiness, cognitive impairment, dizziness, blurred vision, and dry mouth. Self-medication is a common problem that can result in adverse outcomes, especially in older adults. The use of diphenhydramine should be avoided in elderly persons, who are often sensitive to its anticholinergic properties.

Armodafinil (Nuvigil[®]), a central nervous system (CNS) stimulant, is used to improve wakefulness in adults who experience excessive sleepiness because of obstructive sleep apnea, shift-work disorder, and narcolepsy. Most adverse effects are mild to moderate, and include headache, nausea, diarrhea, circadian rhythm sleep disorder, and palpitations. The FDA has refused to approve the use of armodafinil for the treatment of jet lag, and the manufacturer has withdrawn its request for FDA approval.



Conclusion

Jet lag is a sleep disorder common to travelers of all age groups. The disorder is caused by rapid travel across multiple time zones, in which the circadian system is not able to adjust to the rapid shift. The speed of resynchronization of circadian rhythm to the new time zone depends on multiple factors. Jet-lagged travelers may experience disturbed sleep, daytime fatigue, poor performance in mental and physical tasks, decreased alertness, and headache. Several prescription and over-the-counter (OTC) products are used in the management of jet lag. Pharmacists can aid patients in selecting an appropriate, effective treatment.

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