

# Jet Lag

## Current and Potential Therapies

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### INTRODUCTION

Jet lag, also known as circadian desynchrony, is a sleep disorder in which there is a mismatch with the body's natural circadian rhythm and the external environment as a result of 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 is more prolonged than that in young adults.<sup>1</sup>

A multitude of factors, such as the number of time zones crossed and the direction and timing of flights, play a role in the severity of symptoms experienced by travelers. Individual variability accounts for the ability to adapt to a new time zone and the duration of the symptomatic period. Travelers usually experience symptoms after air travel across 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 one week if the change in time zones is greater than eight hours. Eastward travel is associated with a longer duration of jet lag than westward travel. Although frequent desynchrony is a transient disorder, it carries the potential to lead to long-term consequences, as evidenced by epidemiological and animal studies.<sup>2,3</sup> Sequelae have included cognitive deficits, gastrointestinal (GI) disturbances, and an increased risk of cancer, infertility, and heart disease. As the body's internal circadian "clock" adapts to the new time zone, jet lag diminishes.

Strategies to minimize the effects of jet lag include adjusting the sleep schedule according to the new location during the days preceding the trip. This approach may be helpful for travel that lasts for more than a week, but it does not appear useful for short-term trips. Both alcohol and caffeine can adversely affect quality of sleep when they are consumed a few hours before bedtime; caffeine intake should be planned to enhance daytime alertness. When passengers are traveling, they are advised to avoid alcohol, especially while they are being treated for jet lag.

Treatment may include non-pharmacological therapy alone or non-pharmacological therapy combined with nutraceuticals or pharmacological therapy. A non-pharmacological approach, including adequate exercise, hydration, and appropriate timing of exposure to bright light, can aid in the

adjustment to a new time zone. Nutraceuticals and pharmacological therapies include melatonin, melatonin receptor analogues (agonists), non-benzodiazepine hypnotic agents, caffeine, diphenhydramine (e.g., Benadryl, McNeil; Aler-Dryl, Reese), and armodafinil (Nuvigil, Cephalon).

A review of treatments and potential strategies follows.

### 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. Our sleep-wake cycle is thought to be inherently determined, and the explanation for one's reactions to light and darkness lies with the suprachiasmatic nucleus (SCN). The central circadian clock is located in the SCN of the hypothalamus, where light signals from the retina are received. The SCN 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.

The role of melatonin-mediated responses has been studied extensively in hopes of designing a novel therapeutic agent for circadian desynchrony. Some of the effects of activated melatonin type-2 receptors are phase-shift circadian rhythms of neuronal firing in the SCN, inhibiting dopamine release in the retina, inducing vasodilation and inhibition of leukocyte rolling (slowdown) in arterial beds, and enhancing immune responses.<sup>4</sup> It is hypothesized that neuronal clocks within the SCN form a heterogeneous network, wherein a majority of the neurons require periodic synchronization signals to be rhythmic and a small number of neurons or a low connectivity result in desynchrony.<sup>5</sup>

*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-photoc *Zeitgebers* include temperature, social interaction, pharmacological manipulation, exercise, and meal timing.<sup>6</sup>

Blind people with no perception of light frequently show free-running endocrine, metabolic, behavioral, and sleep-wake cycles for their entire lifetime unless a synchronizing treatment is applied and is effective.<sup>7</sup> 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 is to achieve circadian realignment in the most rapid and efficient way possible while minimizing the symptoms of jet lag. The treatment plan de-

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depends on the length of stay in the new time zone. Business travelers, pilots, and flight attendants may experience frequent shifts to changing time zones, and it may be practical for them to remain on their home-based schedule.

Table 1 highlights various agents used for jet lag (page 224).

### 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 and are unable to have exposure to natural sunlight, light therapy may be a viable option. Light synchronizes the body clock by exposing the eyes to an artificial bright light that simulates sunlight for brief periods at planned times during the day. Various modalities include a light box, a lamp, and a light visor.

### Melatonin

In the human body, sleep is initiated during a rise in the concentration of melatonin (*N*-acetyl-5-methoxytryptamine) and during the declining phase of body temperature.<sup>8</sup> Synthesized from serotonin in the pineal gland, melatonin helps to shift human circadian rhythms.<sup>9</sup> 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 conventional afternoon to evening hours of a 24-hour day promotes a phase shift (an advance) in circadian rhythm, thus promoting sleep. When taken in the early morning, exogenous melatonin promotes a phase delay.<sup>10</sup> This promotion of a phase shift and sleep induction by administering melatonin in the afternoon and evening hours can be used to alleviate symptoms of jet lag. Correlating the administration of melatonin with the new time zone may help travelers overcome symptoms.

Melatonin’s utility in the management of jet lag has been the subject of many studies.<sup>8,10,11–22</sup> When making travel plans, particularly over a distance of five or more time zones, travelers should take melatonin on the day of travel at the projected nighttime hour in the new time zone and on subsequent days in the new time zone. In the case of flights that cross seven to eight time zones, it may be beneficial to initiate melatonin one to three days before the intended day of travel in order to better acclimate the traveler to the new time zone.

Arendt et al.<sup>22</sup> conducted the first double-blind, placebo-controlled trial of melatonin in jet lag. The phase-shifting ability of melatonin was evaluated in 17 patients taking an eight-hour eastbound transmeridian flight. Travelers who were randomly assigned to the melatonin group ( $n = 8$ ) were instructed to take 5 mg/day starting three days before the scheduled flight in the early evening (at 6 P.M.) and for four days post-flight at the bedtime hour of the new local time zone (from 10 P.M. to midnight). Subjects receiving melatonin experienced significantly fewer severe symptoms ( $P = 0.009$ ) based on subjective measures, including jet lag ratings, self-recorded sleep parameters, and mood ratings. Melatonin participants also adjusted more rapidly in objective measures, such as assessments of endogenous melatonin levels and cortisol rhythms.

### Melatonin Plus Light Therapy

Combining melatonin and light therapy at appropriate times can mitigate the symptoms of jet lag. The timing of light or melatonin administration should be tailored to the individual’s body clock at the time of departure to gradually shift the body clock to that of the new time zone.<sup>9</sup> For example, with a three- to six-hour eastward time zone change, such as from New York City to Paris, France, travelers should receive bright light on the day before and on the day of departure in order to advance (shift) rhythms. They should avoid evening light exposure, which delays circadian rhythms.

Melatonin should be administered in the mid-afternoon of the departure city (at approximately 3 P.M.) to mimic an approximate bedtime in the destination city (at approximately 9 P.M.). On the day of arrival, travelers should avoid evening light and should take melatonin at the new bedtime in the destination city. Circadian rhythms should advance by one to two hours each day with time zone changes, and melatonin can be taken one to two hours earlier each day until the traveler has adjusted.<sup>9</sup>

A phase delay may be easier if the time zone change is close to 12 hours. In this case, the traveler would want evening light exposure, avoiding daytime light exposure and taking melatonin in the morning to promote a phase delay.

In terms of improving symptoms of jet lag, little to no difference has been shown with various doses of melatonin ranging from 0.5 mg to 5 mg.<sup>23</sup>

Common adverse effects of melatonin have included daytime sleepiness, dizziness, headache, and loss of appetite. It is unclear whether these side effects are a result of the melatonin or the symptoms of jet lag itself.<sup>23</sup> Travelers are also at an increased risk of experiencing hypnotic effects of melatonin at higher doses; as a result, lower doses are preferred for inducing phase shifts without side effects.

### Melatonin Receptor Analogues (Ramelteon and Tasimelteon)

Melatonin receptor analogues (agonists) have not been directly compared with exogenous melatonin therapy in clinical trials. It will be interesting to see whether future studies determine which agents might be more beneficial in the improvement of jet lag symptoms.

#### Ramelteon (Rozerem)

Ramelteon (Rozerem, Takeda), a sedative-hypnotic, has been approved by the FDA for insomnia characterized by difficulty in falling asleep. The dose is usually 8 mg, taken one half-hour before bedtime.<sup>24</sup> The selectivity of ramelteon for melatonin  $MT_1$  and  $MT_2$  receptors, normally acted upon by endogenous melatonin, contributes to sleep promotion and to maintenance of the circadian rhythm underlying the normal sleep-wake cycle.<sup>24</sup>

A randomized, double-blind, placebo-controlled, parallel-group study was conducted to evaluate ramelteon in 110 patients receiving 1 mg/day, 4 mg/day, and 8 mg/day and the drug’s ability to alleviate the sleep-onset difficulties associated with jet lag following eastward transmeridian jet travel across five time zones.<sup>25</sup> Patients receiving ramelteon 1 mg ( $n = 27$ ) experienced a statistically significant decrease in

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mean latency to persistent sleep (LPS) on days 2 to 4. These patients were able to achieve persistent sleep 10.64 minutes faster than the placebo group ( $P = 0.030$ ). The additional treatment groups receiving 4 mg/day ( $n = 27$ ) and 8 mg/day ( $n = 27$ ) showed a tendency toward a reduction in mean LPS, but neither group reached statistical significance ( $P = 0.106$  and  $P = 0.067$ , respectively).

Adverse effects of ramelteon are similar to those of melatonin. It does not appear that ramelteon leads to dependence or withdrawal effects after discontinuation.

### Tasimelteon

Tasimelteon (VEC-162, Vanda/BMS-214778, Bristol-Myers Squibb) is an investigational oral melatonin receptor agonist. In phase 2 and phase 3 studies, tasimelteon decreased transient insomnia that had been induced by an abrupt shift in the sleep-wake cycle.<sup>26,27</sup> Rajaratnam et al. conducted a double-blind, placebo-controlled phase 3 study ( $n = 411$ ) in which it was concluded that tasimelteon, at doses of 20 mg/day ( $n = 100$ ), 50 mg/day ( $n = 102$ ), and 100 mg/day ( $n = 106$ ), improved sleep latency, sleep quality, and sleep maintenance and provided a shift in circadian rhythms after an abrupt advance in sleep time ( $P \leq 0.05$  for all results).<sup>26</sup>

On January 19, 2010, the FDA granted an orphan drug designation status for tasimelteon in non-24-hour, sleep-wake cycle disorder for blind individuals without light perception.

### Non-benzodiazepine Hypnotic Agents

#### Zolpidem (Ambien)

Non-benzodiazepine hypnotics, such as zolpidem (Ambien, Sanofi-Synthelabo), bind the benzodiazepine receptor subunit of the GABA-A receptor complex. This class of medications has a strong hypnotic effect, with weak anticonvulsant and muscle-relaxant properties.

In a multicenter, double-blind, randomized, placebo-controlled, parallel-group study, Jamieson et al.<sup>28</sup> described the use of non-benzodiazepine hypnotic medications in 130 experienced travelers during their regular eastward transatlantic assignments. Patients receiving zolpidem 10 mg/day ( $n = 68$ ) reported longer total sleep times on the first night ( $P < 0.005$ ); fewer awakenings on the first two nights ( $P < 0.003$  for each); and improved quality of sleep on the first, second, and third nights ( $P < 0.004$ ,  $P < 0.004$ , and  $P < 0.056$ , respectively).

Although the FDA has not approved this drug class 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. In this setting, these agents are attractive because of their rapid absorption, short half-life, and inactive metabolites.

When using non-benzodiazepines for the management of jet lag, patients are at risk for experiencing common adverse effects that include dizziness, somnolence, loss of memory, headache, and nausea. When low doses recommended for initiating sleep are used, carryover effects should be minimal the next day.<sup>28</sup> So far, little information is available regarding other non-benzodiazepine hypnotic drugs in the management of jet lag syndrome; however, their effects are likely to mimic those of zolpidem.

### Caffeine

In a systematic review of 13 randomized trials of persons with jet lag or shift-work disorder, caffeine improved concept formation, reasoning, memory, orientation, attention, and perception when compared with placebo.<sup>29</sup> For these reasons, caffeine is a common remedy for treating sleepiness induced by jet lag. Two studies have reviewed its effect after eastward transmeridian travel. Slow-release formulations of caffeine at a dose of 300 mg were used in both studies.<sup>18,30</sup> Pierard et al.<sup>30</sup> demonstrated that slow-release caffeine allowed a quicker resynchronization of hormonal rhythms as a result of mean saliva cortisol concentrations, which were significantly lower than in the placebo group.

A follow-up study by the same authors found that caffeine led to an objective decrease in daytime sleepiness compared with melatonin and placebo, as assessed by multiple sleep latency tests.<sup>18</sup>

### Diphenhydramine (Benadryl)

To date, no studies of diphenhydramine for use in jet lag syndrome have been conducted, even though this is the most common nonprescription antihistamine prescribed for insomnia. Side effects include daytime sleepiness, cognitive impairment, dizziness, blurred vision, and dry mouth and throat. 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)

Armodafinil, a central nervous system (CNS) stimulant, is designed to improve wakefulness in adults who experience excessive sleepiness because of obstructive sleep apnea, shift-work disorder, and narcolepsy.<sup>31</sup>

Rosenberg et al. conducted a phase 3, double-blind, randomized, placebo-controlled study to evaluate armodafinil 50 mg/day and 150 mg/day for the treatment of excessive sleepiness associated with jet lag disorder resulting from east-bound travel in travelers with a history of jet lag symptoms.<sup>32</sup> Patients receiving armodafinil 150 mg/day ( $n = 143$ ) experienced a statistically significant benefit in sleep latency on the Multiple Sleep Latency Test (days 1 to 2: mean, 11.7 vs. 4.8 minutes for placebo;  $P < 0.001$ ). Participants' perceptions of their overall condition in relation to jet lag symptoms on the Patient Global Impression of Severity (PGI-S) were also significant (days 1 to 2: mean, 1.6 vs 1.9 for placebo;  $P < 0.05$ ).

Sleep latency was also significantly increased in the 142 patients receiving armodafinil 50 mg/day (days 1 to 2: mean, 7.7 vs. 4.85 minutes for placebo;  $P < 0.001$ ). However, mean PGI-S scores did not differ in the placebo group ( $n = 142$ ).

Most adverse events were mild to moderate. The most frequently reported events were headache, nausea, diarrhea, circadian rhythm sleep disorder, and palpitations.

In December 2010, Cephalon withdrew its effort to win the FDA's approval to market armodafinil for the treatment of jet lag after it received a second complete response letter from the agency.<sup>33</sup> The company believed that it had met all safety and efficacy endpoints in a clinical study but concluded that further communications with the FDA would not result in an approval

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**Table 1 Agents Used in the Prevention and Treatment of Jet Lag**

Drug	Availability	Class	How Supplied <sup>34</sup>	Dose	Cost <sup>*34</sup>
Melatonin	Over the counter	Nutraceutical	1-, 2.5-, 3-, or 5-mg tablets Sublingual tablets available	0.5–5 mg†	\$7.99 per bottle of 120
Ramelteon (Rozerem)	Prescription only; brand available	Melatonin receptor analogue (agonist)	8-mg tablets	1, 4, or 8 mg five minutes before bedtime‡	\$66.99 for 10 days
Zolpidem (Ambien)	Prescription only; generic available CIV	Non-benzodiazepine hypnotic agent	5- and 10-mg tablets 5- and 10-mg sublingual tablets 5- and 10-mg oral spray 6.25- and 12.5-mg controlled-release tablets	10 mg at bedtime‡	\$14.99 for 10 days
Caffeine	Over the counter	Methylxanthine	250-mg capsules 200-mg tablets	200 mg every three hours p.r.n.	\$6.99 per box of 40
Diphenhydramine (e.g., Benadryl)	Over the counter	Antihistamine	25- and 50-mg capsules 50-mg capsule, liquid-filled 25- and 50-mg tablets	50 mg at bedtime p.r.n.	\$3.49 per box of 48
Armodafinil (Nuvigil)	Prescription only; brand available CIV	Amphetamine-related CNS stimulant	50-, 150-, and 250-mg tablets	150 mg daily‡	\$72.99 for 10 days

CIV = Schedule IV controlled substance; CNS = central nervous system; p.r.n. = as needed.

\* Represented as the dollar amount for 10 days of the first tablet strength listed in the table for prescription-only products.

† The 5-mg dose is commonly used in clinical trials.

‡ Phase 3 clinical trial dose for jet lag; not FDA-approved for jet lag at the time of publication.

Data from Drugstore.com, February 28, 2011.<sup>34</sup>

of its application. The FDA's latest response reiterated concerns that had been raised in March 2010 about using armodafinil for jet lag. At the time, the FDA had questioned the robustness of Cephalon's study data.

### 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 in time zones. The speed of resynchronization of circadian rhythms to the new time zone depends on multiple factors, including the number of zones crossed, the direction of travel, and the traveler's ability to adapt to the new location. Factors exacerbating jet lag symptoms include sleep deprivation, prolonged uncomfortable sitting positions, air quality and pressure, stress, and excessive caffeine and alcohol intake. Jet-lagged travelers may experience disturbed sleep, daytime fatigue, poor performance in mental and physical tasks, decreased alertness, and headache.

A wide array of prescription and over-the-counter (OTC) products have been the focus of study in the management of jet lag. These modalities include light therapy, melatonin, melatonin receptor analogues, non-benzodiazepine hypnotics, caffeine, diphenhydramine, and CNS stimulants such as armodafinil. Depending on the individual patient's sleep-wake cycle and other factors, pharmacists can aid patients in selecting an appropriate treatment. The patient's flight schedule, purpose of travel, physical condition, and individual response to treatment all play important roles. The pharmacist

can evaluate patients' needs and recommend OTC preparations and nutraceuticals or advise patients to consult their primary care physician about available prescription-only products. When making a recommendation, the pharmacist should consider cost, because OTC products are usually considerably less expensive than prescription alternatives (see Table 1).<sup>34</sup>

Finally, the pharmacist should promote the use of non-drug therapy and review the traveler's medication history before recommending a specific pharmacotherapeutic agent.

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