clinical practice

Jet Lag

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 55-year-old physician is planning a trip from Los Angeles to London to attend a scientific conference. His previous trip to Europe was complicated by sleepiness during meetings and difficulty falling asleep and remaining asleep at night. He wants to know what he can do to avoid jet lag. What would you advise?

THE CLINICAL PROBLEM

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Jet lag is a recognized sleep disorder[1] that results from crossing time zones too rapidly for the circadian clock to keep pace. The pathophysiology involves a temporary misalignment between the circadian clock and local time. The circadian clock, located in the suprachiasmatic nucleus of the hypothalamus, is normally synchronized to the solar light–dark cycle and promotes alertness during the day and sleep at night. The clock is slow to reset, so that after time zones have been crossed, the endogenous signals for sleep and wakefulness do not match the local light–dark and social schedules.

The symptoms of jet lag consist primarily of insomnia and daytime sleepiness but can also include dysphoric mood, diminished physical performance, cognitive impairment, and gastrointestinal disturbances. Jet lag is often compounded by nonspecific travel fatigue,[2] which occurs as a consequence of prolonged immobility, irregular sleep times and mealtimes, dehydration, and other factors associated with long-distance air travel, irrespective of the crossing of time zones. Travel fatigue can be reversed within a day or two with adequate diet, rest, and sleep, but symptoms of jet lag persist until the circadian system is realigned. Although jet lag is usually medically benign and self-limited, it may occasionally cause serious misjudgments in business or professional dealings.

An audio version of this article is available at NEJM.org

The incidence of jet-lag disorder is unknown, but it presumably affects a large proportion of the more than 30 million travelers who embark from the United States each year for destinations that necessitate flights across five or more time zones.[3] The intensity and duration of the symptoms of jet lag are related to several factors, which are listed in Table 1. Among very frequent travelers such as flight personnel and international business executives, the disorder may be recurrent or even chronic.

STRATEGIES AND EVIDENCE

There are three treatment strategies for jet lag that are conceptually distinct but that can be combined in practice. These include promoting a realignment of the circadian clock with the use of appropriately timed exposure to light, the administration of melatonin, or both; planning the optimal duration and timing of sleep; and using medication to counteract the symptoms of insomnia or daytime sleepiness.

THERAPEUTIC RESETTING OF THE CIRCADIAN CLOCK

The symptoms of jet lag gradually remit as the circadian system realigns to the new time zone. With the use of the daily cycle in core body temperature as an indicator of circadian time, it has been estimated that the circadian clock resets an average of 92 minutes later each day after a westward flight and 57 minutes earlier each day after an eastward flight.[4] These estimates are supported by a more recent field study that used the timing of melatonin secretion as an indicator of circadian timing.[5]

In principle, realignment can be accelerated by recruiting the clock-resetting mechanisms that, under ordinary circumstances, fine-tune the circadian system to compensate for the difference between the intrinsic period of the circadian clock (which is usually slightly longer than 24 hours) and the 24-hour solar day. Although treatments that are aimed at resetting the circadian clock are more involved, they are attractive because they address the underlying pathophysiology of jet lag.

Optimizing Light Exposure

There is general consensus that the timing of exposure to light is the most important time cue for synchronizing circadian rhythms in humans (as it is in most species). Exposure to light in the evening shifts the clock to a later time, and exposure to light in the morning shifts the clock to an earlier time, thereby compensating for any drift away from a 24-hour cycle (Fig. 1).[6] At some point during the night, there is a crossover point that separates "evening responses" to light exposure (phase delays) from "morning responses" (phase advances). The timing of sleep does not, in itself, reset the clock; however, because people normally sleep in the dark with their eyes closed, sleeping limits the exposure to light and therefore plays an important role in the regulation of the circadian clock.

The intensity and timing of a traveler's exposure to light after arrival at a destination in a different time zone are presumed to be critical factors in determining the speed and direction of re-entrainment. Unplanned exposure to natural daylight in the new location generally facilitates the adaptation of the circadian clock to local time; however, the intensity and availability of light will vary according to the time and season of travel, the local weather, the brightness of interior illumination, and the activity and sleep schedule of the traveler. These factors can result in considerable variability in the direction and speed of re-entrainment. Nevertheless, a traveler may be able to accelerate re-entrainment by intentionally seeking out bright light at the optimal times of the day. A simple recommendation for travel across up to eight time zones is to seek exposure to bright light in the morning after eastward travel and in the evening after westward travel.

It may also be useful to avoid light when exposure would impede adaptation. For example, after eight or more time zones have been crossed, sunlight that would ordinarily be interpreted by the circadian system as "dawn" may now be interpreted as "dusk" (and vice versa). Thus, staying indoors for the first few hours of daylight after long eastward flights or for a few hours before dusk after long westward flights may be indicated.[2,10,11] After a few days, the circadian system will have shifted sufficiently that avoidance of light can be discontinued. If avoiding bright light is impractical, wearing low-transmittance sunglasses may be a useful alternative, as suggested by studies that have simulated shift work.[12] More specific recommendations for exposure to and avoidance of light are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. However, current treatment recommendations for resetting the circadian clock that are based on the timing of light exposure rely heavily on models of circadian regulation that have been developed from laboratory studies and must be considered to be provisional, pending additional testing in randomized clinical trials.

In some cases, the direction of re-entrainment is the opposite of the direction of travel — a situation that can prolong symptoms of jet lag.[10] This may be more likely to occur if circadian orientation was atypical before departure — for example, in the case of a night-shift worker or a traveler who was still jet-lagged from an earlier flight. It may also be more common after long eastward flights[5,13] because advancing the clock is usually more difficult than delaying it. Some experts recommend that all flights that cross more than 8 to 10 time zones be treated as if they were westward.[2]

Melatonin Administration

Melatonin is a hormone that is secreted for about 10 to 12 hours at night; secretion of melatonin is synchronized to the light–dark cycle by the circa-

Table 1. Factors That Contribute to Jet Lag.

Factor	Contribution to Jet Lag
No. of time zones crossed	The degree of circadian misalignment is proportional to the number of time zones crossed; nonspecific travel fatigue occurs with long-distance travel whether or not times zones are crossed and often compounds symptoms of jet lag.
Direction of travel	For most people, it is more difficult to travel east than west because the endogenous period of the body clock is typically longer than 24 hours and it is therefore easier to lengthen the day than to shorten it; however, some people, especially "morning types" (whose endogenous period may be shorter than 24 hours), may find eastward travel easier.
Sleep loss during travel	Sleep loss is almost inevitable with overnight travel, but it may be attenuated with business-class or first-class seating; acute sleep loss can be made up with adequate sleep after arrival, but symptoms of jet lag will probably persist until circadian realignment has occurred.
Availability of local time cues	Exposure to natural light at the destination is the most important factor for re-entrainment of the circadian clock, but it varies with the location, the time of year, and the activity of the traveler; exposure to bright light at the "wrong" phase of the circadian cycle can inhibit re-entrainment of the circadian clock.
Ability to tolerate circadian misalignment	There are individual differences in the ability to tolerate phase misalignment, but in general, tolerance appears to decrease with increasing age.

dian clock. The hormone can be considered to be a darkness signal, with effects on circadian timing that are the opposite of the effects of exposure to light[7,8]; that is, when melatonin is taken in the evening (before the onset of its endogenous secretion), it resets the body clock to an earlier time, and when it is taken in the morning (after endogenous levels have fallen), it resets the clock to a later time (Fig. 1). Melatonin receptors on the suprachiasmatic nucleus, the anatomical site of the circadian clock,[14] probably mediate the clock-resetting effects of exogenous melatonin. Most of the benefits of melatonin with respect to jet lag are probably related to its clock-resetting effects, but melatonin may also have some direct hypnotic activity, especially at higher doses (1 mg or more).

The administration of melatonin is the most extensively studied treatment for jet lag.[9,15] Of 11 double-blind, placebo-controlled trials,[16-26] 8 showed a significant benefit of melatonin with respect to symptoms of jet lag as rated by the study participants. Two of the studies that did not show a benefit of melatonin may have been underpowered,[19,25] and one involved subjects whose baseline circadian phase may not have been appropriate[26]; subjects from Norway were treated on the homeward leg of their trip after having spent just 5 days in New York, during which they may not have fully adapted to local time. The results of several field studies of melatonin administration that have monitored the circadian phase[19,27] have provided some support for the assumed correlation between the reduction of symptoms and accelerated realignment of the circadian clock, but this association requires further investigation.

A meta-analysis[15] of four trials that used similar outcome measures[16-19] estimated the magnitude of the benefit from melatonin (administered at a dose of 5 or 8 mg). On a 100-point visual-analogue scale (with higher scores indicating more severe jet lag), the weighted mean average global jet-lag score was significantly lower after treatment with melatonin than after receipt of a placebo ($P<0.001$); after eastward travel, the scores were 31 and 51, respectively, and after westward travel, the scores were 22 and 41, respectively.

In a majority of studies of melatonin, the hormone was administered at bedtime after an eastward flight.[16,18,22,23,25,26] However, bedtime may not be the optimal time to take melatonin after a westward flight that crosses fewer than six to eight time zones, since the administration of melatonin has the least phase-shifting effect when it overlaps with endogenous secretion.[7,8] It may be preferable to take a low, short-acting dose (0.5 mg or less) later in the night.

The most common dose of melatonin that was used in the randomized trials was 5 mg.[16,17,19-21,25] In one trial that compared a 5-mg dose with a 0.5-mg dose, the efficacy of the two doses was similar, although subjects rated the higher dose as more sleep-promoting.[22] A single trial in which melatonin was compared with the hypnotic agent zolpidem (administered at a dose of 10 mg) and with melatonin and zolpidem combined showed that zolpidem alone seemed to be the most effective of the study treatments in reducing self-rated symptoms of jet lag; the combination of the two drugs was associated with a higher incidence of daytime sleepiness and confusion than either drug alone.[23]

In several of the studies,[16,17,20,21] melatonin was given for a few days before departure, at a time that coincided with bedtime at the destination, but it remains unclear whether anticipatory treatment provides a substantial advantage over treatment that is initiated after arrival at the destination.

Melatonin is most commonly marketed in the United States as a nutritional supplement in a 3-mg formulation. It is not approved by the Food and Drug Administration (FDA) for any indication. However, no major or consistent adverse events have been reported in the clinical trials that have been performed to date.

STRATEGIC SCHEDULING OF SLEEP

A simple way to minimize jet lag, especially in the case of trips of short duration, is to try to maintain the sleep–wake schedule from home after arrival at the destination,[28] but this strategy is often incompatible with desired social activities or business obligations.

Shifting one's sleep schedule by 1 or 2 hours toward congruence with the destination time zone before departure may shorten the duration of jet lag. More substantial adaptation before travel, through a combination of rescheduling of sleep and artificial exposure to light, has been shown in simulation studies to augment phase-shifting and reduce symptoms of jet lag,[11] but this strategy requires considerable planning and discipline.

First-class or business-class accommodations that facilitate sleep will probably reduce the travel-fatigue component of jet travel. However, most travelers will be sleep-deprived after an overnight flight and will require extra (recovery) sleep on the first day or two after arrival. On subsequent days, short naps are effective in reducing daytime sleepiness, whereas longer daytime naps can undermine nighttime sleep, as well as reduce exposure to the re-entraining effects of light. Even with adequate nighttime sleep, daytime sleepiness may persist until the circadian system is realigned.

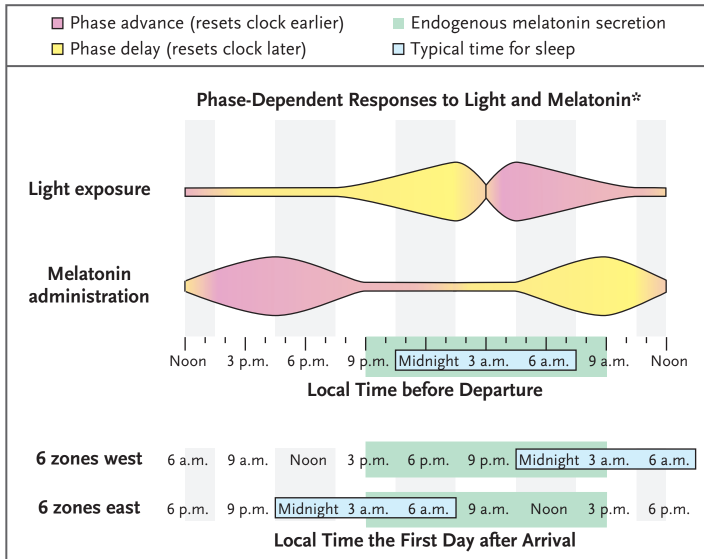

Figure 1. Effects of Light and Melatonin on Resetting of the Circadian Clock.

The schematic diagram shows the phase-dependent effects of exposure to bright light and the administration of melatonin on the circadian clock, as derived from laboratory studies.[6-8] A typical circadian orientation at home (before departure) is assumed — that is, sleep between 11 p.m. and 7 a.m. and melatonin secretion (a biomarker for the nocturnal phase of the circadian cycle) from 9 p.m. to 9 a.m. Under these conditions, exposure to bright light in the evening and the first part of the night would be expected to reset the clock later (a phase delay), whereas exposure to bright light in the last part of the night and the morning would reset the clock earlier (a phase advance). The effects of melatonin administration are approximately the inverse of the effects of light — that is, administration of melatonin in the afternoon and evening shifts the clock earlier, and administration of melatonin in the morning shifts the clock later. In the case of exposure to light, the magnitude of a response is largest in the middle of the night, when exposure is usually minimal. In the case of melatonin administration, the magnitude is largest during the day, when endogenous secretion is minimal. On the first day after time zones are crossed, the circadian clock remains oriented to the departure location (as reflected in the timing of melatonin secretion), and therefore the local times for sleep (and wakefulness) are misaligned with the circadian system — the underlying pathophysiology of jet lag. Moreover, the responses to light exposure and melatonin administration continue to be determined by the original (home-base) phase of the clock. Exposure to sunlight after arrival at the new destination now is more likely to occur at times when the circadian system is the most sensitive to light, thereby inducing phase shifts that reset the clock to local time. As the circadian clock is re-entrained, the response patterns are gradually realigned with the new orientation. The relative magnitude of the response in relation to the phase of the circadian cycle is portrayed. The response to light exposure will also depend on the intensity and duration of exposure, wavelength, pattern of exposure, and possibly history of light exposure; the response to melatonin may be dose-dependent.[9] Recommendations regarding the use of exposure to bright light and treatment with melatonin to treat jet lag are derived from the time-dependent effects illustrated here.

PHARMACOTHERAPY

Hypnotic Agents

A short course of hypnotic medication has been shown in randomized trials to reduce insomnia related to jet lag.[23,29-33] In a randomized, placebo-controlled trial involving 133 persons, the use of zolpidem (10 mg at bedtime) for 3 to 4 nights after eastward travel across five to nine time zones significantly improved total sleep time and sleep quality while reducing awakenings from sleep.[33] The use of a hypnotic agent may also be helpful during an overnight flight, since a traveler may have difficulty sleeping while seated in a cramped, semirecumbent airplane seat. Because there is limited opportunity to sleep during a flight, a hypnotic medication that has only a 2- to 3-hour duration of action (e.g., zaleplon) is preferred.

A decision to use hypnotic agents during travel should take into account their potential adverse effects, including amnesia and confusion[34]; for example, dramatic global amnesia was reported in several cases in which triazolam was used to promote sleep during jet travel.[35] Patients who have not previously taken hypnotic medications might be advised to take a test dose at home before using them during travel. Another factor to consider when hypnotic agents are used is that the immobility induced by a hypnotic medication might be expected to further increase the already elevated risk of deep-vein thrombosis that is associated with air travel.[36]

Agents That Promote Alertness

Increased consumption of caffeine may counteract the daytime sleepiness associated with jet lag. In a double-blind, controlled trial, slow-release caffeine (300 mg) increased alertness and reduced other symptoms of jet lag after eastward flight across seven time zones.[24] The primary risk of caffeine consumption is an exacerbation of the insomnia associated with jet lag.

Armodafinil, a drug that is currently approved by the FDA for the treatment of narcolepsy but is not approved for the reduction of symptoms of jet lag, was recently shown to improve wakefulness after air travel across six time zones (from the eastern United States to France).[37] In a trial involving 427 subjects who were randomly assigned to armodafinil at a dose of 50 mg, armodafinil at a dose of 150 mg, or placebo, all administered at 7 a.m. for 3 consecutive days after arrival, both armodafinil groups had a reduction in self-rated daytime sleepiness and an increase in alertness, as measured by the time it took for the subjects to fall asleep during scheduled daytime nap trials that were performed on the first 2 days after arrival. There was a higher incidence of headache, nausea, and vomiting among the subjects who received armodafinil than among those who received placebo. Modafinil, a drug that is closely related to armodafinil, could be expected to have similar effects, although it has not been evaluated in a clinical trial.

AREAS OF UNCERTAINTY

Additional field studies that use state-of-the-art measures of the circadian phase[38,39] are needed to elucidate the natural course of circadian re-entrainment after time-zone displacement and the factors that mediate it, such as exposure to natural light, baseline circadian phase before departure, age, and sex. Randomized, controlled trials are needed to test the efficacy of planned exposure to or avoidance of light. The optimal treatment for travelers who cross 8 to 12 time zones remains perplexing, since some studies have shown that re-entrainment can occur by either advances or delays[5,10]; the recommendation for treating all such travel as if it were westward travel[2] needs to be tested in field studies.

The optimal dose of melatonin is uncertain. For the purpose of resetting the circadian clock, the timing of the administration of melatonin (relative to the phase of the circadian clock) is probably more important than the dose, but this requires further study. Additional studies are needed to provide data on the optimal timing of the administration of melatonin after westward travel, when a bedtime dose may not be optimal. Clinical trials are warranted to evaluate the new melatonin agonists that may have clock-resetting effects[40,41] and to assess the benefits and risks of combining different agents to treat the syndrome of jet lag.[23]

Data on the effects of other, nonpharmacologic interventions for jet lag are scarce. A single study of the Argonne diet (which involves alternating days of "feasting" on high-protein breakfasts and lunches and high-carbohydrate dinners with days of caloric restriction) showed some benefit in reducing the symptoms of jet lag but lacked an appropriate control group.[42] Exercise has also been proposed to reduce the symptoms of jet lag but

Table 2. Recommendations for Minimizing Jet Lag and Travel Fatigue.

Strategy	Traveling Westward	Traveling Eastward
Before travel		
Begin to reset the body clock	If possible, shift the timing of sleep to 1–2 hr later for a few days before the trip; seek exposure to bright light in the evening	If possible, shift the timing of sleep to 1–2 hr earlier for a few days before the trip; seek exposure to bright light in the morning
Try to get an adequate amount of sleep	Do not leaving packing and other travel preparations to the last minute; if possible, schedule a flight at a time that will not cut short the sleep time before travel	
In flight		
Try to optimize comfort	Travel in business class or first class, if financially feasible	
Drink judiciously	Drink a lot of water to remain hydrated; minimize consumption of caffeine if you expect to sleep; do not drink alcohol if you intend to take a sleeping pill during the flight	
Use a sleeping medication, if necessary	Consider a short-acting sleeping pill (e.g., zaleplon [Sonata, King Pharmaceuticals] at a dose of 5–10 mg) to promote sleep during the flight; a longer-acting sleeping pill ([e.g., zolpidem [Ambien, Sanofi-Aventis] or eszopiclone [Lunesta, Sepracor]) could result in grogginess on arrival; a sleeping pill should not be taken if there is a risk of deep-vein thrombosis, and it should not be combined with alcohol	
Take measures to avoid deep-vein thrombosis	Because sitting immobile for a long time can increase the risk of a blood clot, change positions frequently and walk around when possible; if you are prone to blood clots, consult a physician, since a more specific preventive measure may be needed (e.g., using anti-embolism stockings)	
On arrival		
Be prepared for changes in sleep pattern	Expect to have trouble staying asleep until you have become adapted to local time	Expect to have trouble falling asleep until you have become adapted to local time
Take appropriate naps	If you are sleep-deprived because of an overnight flight, take a nap after arrival at your destination; on subsequent days, take daytime naps if you are sleepy, but keep them as short as possible (20–30 min) in order not to undermine nighttime sleep	
Use sleeping medication, if necessary	Consider taking a sleeping medication (e.g., zolpidem [Ambien] or eszopiclone [Lunesta]) at bedtime for a few nights until you have adjusted to local time	
Take melatonin	To promote shifting of the body clock to a later time, take 0.5 mg (a short-acting dose) during the second half of the night until you have become adapted to local time	To promote shifting of the body clock to an earlier time, take 0.5–3 mg at local bedtime nightly until you have become adapted to local time
Seek appropriately timed exposure to light	Seek exposure to bright light in the evening	Seek exposure to bright light in the morning
After crossing more than eight time zones, avoid light at times when it may inhibit adaptation*	For the first 2 days after arrival, avoid bright light for 2–3 hours before dusk; starting on the third day, seek exposure to bright light in the evening	For the first 2 days after arrival, avoid bright light for the first 2–3 hr after dawn; starting on the third day, seek exposure to bright light in the morning
Drink caffeinated drinks judiciously	Caffeine will increase daytime alertness, but avoid it after midday since it may undermine nighttime sleep	

* This strategy is based on the theory that after a person crosses eight or more time zones, the circadian system may initially misinterpret “dawn” as “dusk” (or vice versa).

has not been studied in clinical trials, and even strenuous exercise has modest effects on circadian rhythms.[43,44]

GUIDELINES

The guidelines for the management of jet lag issued by the American Academy of Sleep Medicine[45] support the use of melatonin as a standard treatment and identify the scheduling of sleep times, appropriately timed exposure to light, and hypnotic and stimulant pharmacotherapy as reasonable treatment options. The recommendations in this article are generally consistent with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

Persons who are planning to travel across several time zones can be provided with strategies to minimize the symptoms of jet lag (Table 2). In the case of the traveler described in the vignette, I would recommend that, before departure for London from Los Angeles, he gradually advance his sleep schedule by 2 hours and seek exposure to bright light on awakening. After his arrival at his destination, I would recommend that he walk in the bright sunlight and drink a caffeinated beverage each morning. I would also recommend that he take melatonin, at a dose of 3 mg (the dose that is most commonly available) at bedtime, for 3 to 4 days to accelerate phase shifting. If melatonin alone is insufficient to facilitate sleep, the addition of a hypnotic agent may be justified. On his return, I would advise him to seek exposure to bright light in the evening and to take a low dose of melatonin (0.5 mg) if he awakens before 5 a.m.

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