

# The pathophysiology of jet lag

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**Summary** Jet Lag Disorder (JLD) is a recognized circadian rhythm sleep disorder characterized by insomnia or excessive daytime sleepiness (and sometimes general malaise and somatic symptoms) associated with transmeridian jet travel. It is a consequence of circadian misalignment that occurs after crossing time zones too rapidly for the circadian system to keep pace. The thesis of this review is that a rational treatment approach for jet lag can be grounded in an understanding of the biology of the human circadian timekeeping system. An overview of circadian rhythm physiology is presented with special emphasis on the role of light exposure and melatonin secretion in the regulation of circadian timing. Both timed light exposure (or avoidance) and exogenous melatonin administration have been recruited as treatment modalities to accelerate circadian realignment, based on an understanding of their role in circadian physiology. In addition to circadian misalignment, other contributing causes to jet lag are considered including travel-related sleep deprivation and fatigue. Clinical field trials that have tested the application of circadian rhythm based interventions are then reviewed.

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## Introduction

Jet Lag Disorder (JLD) is recognized by the American Academy of Sleep Medicine's diagnostic manual under the section on Circadian Rhythm Sleep Disorders.<sup>1</sup> The diagnostic criteria are straightforward:

- A. There is a complaint of insomnia or excessive daytime sleepiness associated with transmeridian jet travel across at least two time zones.
- B. There is an associated impairment of daytime function, general malaise, or somatic symptoms such as

gastrointestinal disturbance within one or two days after travel.

- C. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

In essence, JLD is a consequence of circadian misalignment that occurs after crossing time zones too rapidly for the circadian system to keep pace. The circadian clock is slow to reset; it has been estimated that it takes about a day per time zone for the circadian system to resynchronize (although there may be considerable individual variability). In addition to circadian misalignment, long distance jet travel is compounded by travel fatigue and insufficient sleep from sitting for a long periods of

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time, usually in an uncomfortable upright position in a cramped airline seat. Overindulgence in coffee or alcohol may amplify the symptoms.

The intensity and duration of the jet lag symptoms are related to a number of factors: (1) the number of time zones crossed, (2) the direction of travel, (3) the ability to sleep while traveling, (4) the availability and intensity of local circadian time cues upon arrival, and (5) individual differences in tolerance to circadian misalignment.

While jet lag is generally benign and self-limited, feeling alert, productive, and cheerful are important goals for travelers, and, therefore, treatment is warranted, if it is safe and effective. Sometimes serious, unfortunate, and even dangerous consequences can result from jet lag, including untoward business, diplomatic or military decisions. Athletes, who compete in international sports requiring optimal performance, have understandable concerns with the effects of jet lag. In professional travelers such as flight personnel, diplomats, and international business executives, the disorder may be recurrent or even chronic.

The thesis of this paper is that a rational treatment approach to jet lag can be grounded in an understanding of the biology of the human circadian system. To that end, the paper will review some basic concepts of circadian physiology including a brief description of the “opponent process model” of sleep regulation that explains the consequences of circadian misalignment. This will be followed by a discussion of some of the strategies used to assess circadian time (phase) in humans, thereby enabling an operational measure of circadian alignment (or misalignment). This is followed by a review of the role that light exposure and melatonin play in the regulation of circadian timing, and how timed light exposure and melatonin administration can be recruited as treatment modalities to accelerate circadian realignment. Finally, some of the field trials that have tested the practical application of circadian based intervention modalities will be reviewed. These field studies can demonstrate how circadian rhythm science is being translated into clinical practice.

### **Circadian misalignment: the underlying pathophysiology of jet lag disorder**

Mammalian circadian (*circa* meaning *about* and *dian* meaning *day*) rhythms are generated by *clock gene*-mediated transcription–translational feedback processes within individual neurons of the paired suprachiasmatic nuclei (SCN) located in the hypothalamus. The summed output from these neurons produces a timing signal that is broadcast widely in the brain and modulates daily rhythms in sleep propensity and alertness, core body temperature, and the secretion of certain hormones such as melatonin and cortisol.

If normal people are isolated from all time cues, circadian rhythms will typically “free-run” on a cycle slightly different than 24 h. These free-running rhythms express the intrinsic circadian period of the SCN circadian pacemaker without the corrective adjustments derived from environmental time cues. Using a “forced desynchrony protocol,”

Czeisler et al.<sup>2</sup> have estimated that in normally sighted people, the average human circadian period is 24.18 h. with a range 23.9–24.4 h. Other estimates of circadian period derived from time isolation experiments, or from assessment of circadian period in totally blind people with free-running rhythms (explained in more detail below) indicate that the endogenous circadian period is longer, averaging about 24.5 h.<sup>3,4</sup> In any case, precise synchronization (entrainment) of the circadian system to the 24-h day requires regular adjustments derived from exposure to environmental time cues, originally termed *zeitgebers* (timegivers).

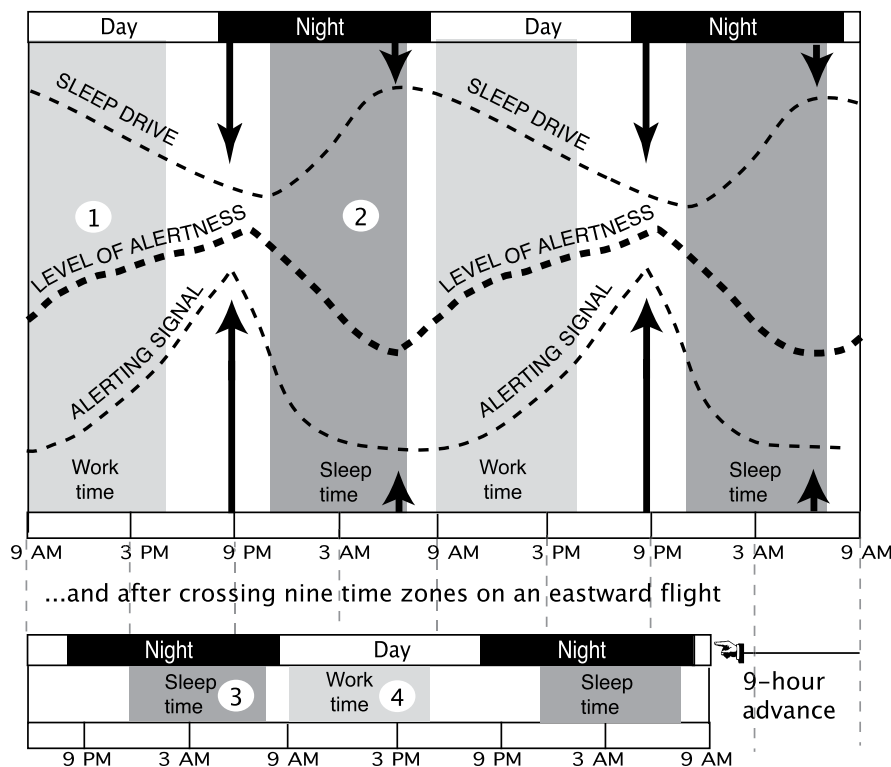
JLD shares the pathophysiologic mechanism of all circadian rhythm sleep disorders; namely, a mismatch between endogenous circadian rhythms (generated by the circadian clock in the SCN) with the desired (or required) schedule for sleep and wake. Current theories of sleep regulation such as the opponent process model as formulated by Edgar and colleagues<sup>5</sup> explain the interaction between circadian and homeostatic factors on sleep and alertness. Homeostatic sleep drive refers to the process in which sleep tendency increases with the duration of prior wake; thus, homeostatic sleep drive begins to accumulate immediately upon awakening and gradually accumulates as the day progresses. However (according to the opponent process model) this accumulating sleep drive is not manifested as overt sleepiness because, during the day, the circadian system generates an alerting signal that counteracts (opposes) the expression of sleep drive. Then at the end of the day, an hour or two before habitual bedtime, the circadian alerting signal subsides and the balance between the two opponent processes shifts, and a person begins to feel sleepy. With the onset of sleep, the accumulated homeostatic sleep drive begins to dissipate, and with a full night of sleep, will be gone by morning. For normally entrained individuals living according to a regular, conventional schedule, the homeostatic and circadian systems are synchronized with each other and with the 24-h solar day–night cycle.

In JLD, the homeostatic and circadian processes are out of alignment. This results in an inappropriately timed circadian alerting signal that shortens sleep duration and reduces sleep quality. Furthermore, the effects of circadian misalignment are compounded by travel-related interruptions to sleep that increase sleep debt. Homeostatic sleep drive can accumulate over several days if jet lag insomnia persists. Moreover, with circadian misalignment, the circadian alerting signal is reduced or is absent during the day; thus, during the waking hours, homeostatic sleep drive may be unopposed, and sleepiness may emerge even when an individual has obtained what would seem to be a sufficient amount of sleep. The various consequences of circadian misalignment are illustrated in Fig. 1 and discussed in the accompanying legend.

### **Phase markers — determining circadian time**

Research on circadian rhythms in humans depends on the availability of relevant assessment techniques. One of the most important measurements is the phase of the internal circadian clock; in other words to assess “what time it is in

## Opponent process of sleep regulation, on home schedule ...



**Figure 1** The opponent process model of sleep regulation explains symptoms of jet lag. The opponent process model of sleep regulation, proposed by Edgar et al.,<sup>5</sup> is illustrated in a double-plotted hypothetical diagram. According to the model (illustrated in the upper panel), an individual's level of alertness (relative sleepiness) is a vector sum derived from the opposing forces of sleep drive that accumulates in proportion to the duration of prior wakefulness (shown as a downward force), and an alerting process, generated by the circadian pacemaker in the SCN (shown as an upward force). During the day (upper panel, #1), sleep drive accumulates, but is counteracted by an opposing alerting signal. In the early evening, the circadian alerting signal peaks and, even though sleep drive is strong, initiating sleep may be difficult. Prior to bedtime, the alerting signal recedes, sleepiness emerges, sleep commences, and sleep drive dissipates (#2). At the time of final awakening, sleep drive is at a minimum. After sleep inertia has receded, the daytime level of alertness is restored to a normal zone. The lower pane illustrates the consequences of circadian misalignment upon arrival after eastward flight across nine time zones. Because clock resetting has yet to occur, the circadian alerting process remains anchored to the time zone of departure. The conventional time for sleep at the new location (#3) coincides with an elevated alerting signal (timed to home base) and sleep is thereby shortened and non-restorative. The conventional time for work (or sightseeing) at the new location (#4) is coincident with a recession of the circadian alerting signal; consequently, accumulated sleep drive (compounded by insufficient sleep during the flight) is unopposed by the circadian alerting process, and intense daytime sleepiness is to be expected.

the brain." To that end, major efforts have been made to develop markers of circadian phase ("the hands on the clock.") suitable for human investigation. One can, in principle, monitor any physiological variable that is modulated by SCN output, provided that there is a way to factor out evoked, non-circadian, influences that would mask the underlying rhythm. The timing of the sleep-wake cycle itself is a rough indicator of circadian phase, but is also influenced by homeostatic sleep drive, as well as volition and many other factors. Notwithstanding, wake up time has been shown to provide a fair estimate of circadian phase in normal subjects who are entrained to a 24-h day but allowed to sleep on a self-determined schedule.<sup>6,7</sup>

In the past, measurement of the core body temperature (CBT) rhythm has been used more extensively than any other circadian phase marker, but the CBT rhythm is readily masked by the effect of activity, food intake, and sleep on

body temperature. Consequently, valid estimates of CBT rhythms require that a subject be kept awake, at bed rest, and fed equally distributed small meals for at least 24 h — a procedure termed the "constant routine protocol".<sup>8</sup> The constant routine protocol has been useful for research, but is very labor intensive and expensive. As an alternative, mathematical adjustments to the temperature rhythm analysis can minimize the masking effects on CBT assessment.<sup>9,10</sup>

Melatonin is a hormone that has been linked to the circadian system since early in evolution. In humans, it is actively secreted by the pineal gland for about 10–12 h at night, in the dark. The timing of melatonin secretion by the pineal gland is currently the most popular strategy for determining circadian phase because of its convenience, sensitivity, and documented validity. The transition from low, daytime levels to robust nocturnal secretion — the

“melatonin onset” – provides a high-resolution marker of circadian phase and is relatively convenient because serial sampling can be done in the evening (at least for subjects who are normally entrained).<sup>11</sup> However, other points on the melatonin profile (e.g., midpoint of secretion) can also be used as a phase marker. Melatonin secretion is suppressed by light exposure (a masking effect) so that samples need to be obtained in dim light conditions; thus the procedure has become known as the *dim light melatonin onset* (DLMO). When both CBT (using constant routine conditions) and DLMO have been assessed concurrently as phase markers, the correlation is high; for example, in a phase shifting study using bright light, the correlation between the two phase markers was 0.97 ( $P < 0.0001$ ;  $N = 23$ ).<sup>12</sup> The determination of melatonin rhythms has been facilitated by the availability of immunoassays that are sufficiently sensitive and specific so that concentrations of melatonin can be measured in plasma or saliva, or its metabolite 6-sulphatoxymelatonin (aMT6s) in urine.

Normally, circadian rhythms are not only synchronized to the external environment, but also to each other. In some instances, sleep and wake time may be early or late compared to a conventional schedule, but if the timing is congruent with the underlying sleep propensity rhythm generated by the SCN, it need not be considered abnormal. Once the circadian phase of the circadian pacemaker is known (for example, by measuring the DLMO or CBT nadir), the interval between it and other cyclic variables of interest can be quantified. This interval between two daily events (e.g., DLMO and bedtime) is called the *phase angle*, even if it is expressed in hours and minutes instead of degrees ( $24\text{ h} = 360\text{ degrees}$ ). A lack of congruence can be expressed as the difference in phase angle from normative data, from a control group, or from the same subject at a preceding time. At the present time, concurrent measurements of circadian phase and other cyclic variables are done mainly in laboratory experiments. As the DLMO becomes more widely used, it is likely that phase angle assessments will be obtained more often in field studies and clinical practice. In recovery from JLD, full adaptation to local time can be said to occur when all the overt rhythms are in synchrony with local clock time and with the endogenous circadian pacemaker.

In summary, research on normal human circadian rhythms (as well as circadian rhythm disorders) has been enhanced by methods to accurately tell “circadian time.” These techniques have been used mainly in laboratory-based research, and to some extent for research in the field. In the future, monitoring of phase markers is likely to become more available for general clinical use.

### The role of solar light exposure for entrainment of circadian rhythms

Circadian rhythms have evolved so that animals and plants can alter their physiology and behavior in anticipation, rather than in response, to the predictable daily alternations in environmental conditions related to the solar light–dark cycle. Therefore, in almost all species, the most important time cue for entrainment of circadian rhythms is the timing of dawn and dusk. Initially it was thought that humans might be the exception to this rule because social

and informational time cues were more well developed. However, subsequent research has shown that for the human species, as for almost all other living organisms, light exposure is the most important environmental timing cue. Prior to the development of artificial illumination, solar light exposure was probably the only important cue.

Further evidence for the importance of the daily light dark cycle for entrainment comes from the finding that totally blind people (without light perception) who are living in normal society, with access to apparent time cues such as clocks and social interactions, and who are maintaining a conventional sleep–wake cycle, nevertheless, will often have free-running rhythms, similar to sighted people living in total temporal isolation.<sup>4,13</sup> In totally blind people, who have free-running rhythms, the average circadian period is 24.5 h with a range of 23.9–25.1 h.<sup>4</sup>

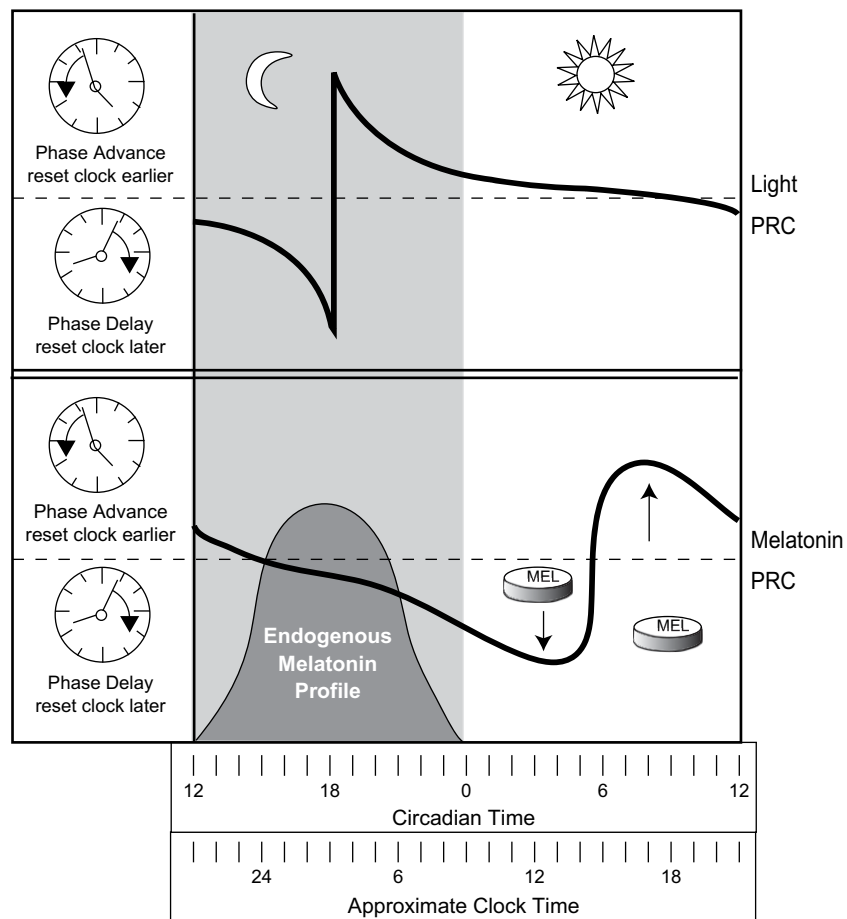
Certain non-photoc time cues, regular activity or meals may have some influence on circadian timing, but the effect is weak compared to the potency of light exposure. The timing of sleep indirectly (but importantly) influences circadian rhythms because people ordinarily sleep at night in a dark space with eyes closed, thereby “gating” the effect of light.

The clock-resetting (phase adjusting) effects of light are critically dependent on the timing of exposure. In normally entrained individuals, light exposure in the morning resets the body clock to an earlier time (produces a phase advance), whereas light exposure in the evening resets the body clock to a later time (produces a phase delay). These differential effects of timed light exposure on the circadian system can be plotted as a phase response curve (PRC) as shown in Fig 2. The *advance and delay* adjustments of morning and evening light maintain the day-to-day circadian period very close to 24.0 h.

Laboratory studies have shown that the magnitude of light-induced phase shifts become greater as they get closer to the inflection point of the PRC where the effect of light exposure abruptly changes from a delay to an advance (Fig. 2.). For normally entrained individuals, this inflection point averages around 5 a.m., but depending on the individual and their habitual schedule, it can be a few hours earlier or later. Before the advent of artificial illumination, the most sensitive portions of the PRC (during the night) were rarely exposed to bright light because they occurred when a person was asleep in the dark. On the other hand, in the modern era, with the advent of brightly lit interior spaces at night, and especially after travel over multiple time zones, the sensitive portions of the PRC are exposed. In normally entrained individuals, light-induced phase shifts are minimal at mid-day – sometimes called the “dead-zone” of the light PRC.

Recently, non-rod, non-cone photoreceptors located in the ganglion cells of the retina have been identified as especially important for the phase-resetting effects of light.<sup>14</sup> These novel non-visual circadian photoreceptors containing the photopigment melanopsin are most sensitive to wavelengths in the blue–green spectrum. This implies that blue–green light exposure may be the most efficient wavelength to shift the circadian system; but there is considerable redundancy in the circadian photoreceptive system so that rods and cones play a role as well.

Bright solar intensity light (3000–10,000 lux), generated by specially constructed fixtures, has been used experimentally and therapeutically to produce robust circadian



**Figure 2\*** Schematic phase response curves (PRC) for light and melatonin administration. The effects of light and melatonin are dependent on the timing (phase) of administration, a relationship that can be plotted as a phase–response curve (PRC). Light exposure late in the day or melatonin administration in the morning will cause the circadian clock to shift later (a phase delay); on the other hand, light exposure in the morning or melatonin administration late in the day will cause the circadian clock to shift earlier (a phase advance). Both light and melatonin PRC’s have an inflection point, the crossover time between advances and delays. According to convention, circadian time 0 is the beginning of the light phase (daytime) and circadian time 12 is the beginning of the dark phase (nighttime). \*Reprinted with permission from Sack RL. *Treatment of circadian rhythm sleep disorders*. In: Kashida C, editor. *Handbook of sleep disorders*. 2nd edition, New York: Taylor and Francis; 2009.

phase shifts. However, even modest intensities of light (100–550 lux) that are typical for illuminated interior spaces can produce some phase shifting, especially in subjects who have been previously maintained in a constant dim light environment.<sup>15</sup> Also, intermittent bright light exposure can produce about as much phase shifting as continuous exposure.<sup>16</sup> In addition to absolute intensity, light exposure history and the contrast of the light exposure with the background intensity, appears to be important. An experiment that reported phase resetting with light exposure to the skin<sup>17</sup> has not been replicated.<sup>18,19</sup>

In summary, light exposure is the most important environmental time cue involved in circadian phase-shifting that is required to achieve and maintain normal circadian synchrony. The effects of light are dependent on intensity, timing, wavelength, pattern (intermittent or continuous), duration, exposure history, and the level of contrast with background light exposure, but timing and intensity are probably the two most important dimensions.

### Melatonin and the circadian system

Melatonin is a hormone actively secreted by the pineal gland for about 10–12 h at night in the dark. The precise function of melatonin in humans (if any) is unknown, but in general it seems to promote modulations of physiology and behavior that are appropriate to a nocturnal state. For example in diurnal species, melatonin plays some role in reducing core body temperature at night. On the other hand, melatonin secretion is not necessarily associated with sleep since in nocturnal species such as rodents, melatonin secretion coincides with the activity phase of the daily cycle.

A circuitous, multi-synaptic pathway from the SCN to the pineal controls the timing of melatonin secretion. Efferent projections from the SCN leave the skull, descend into the thoracic spinal cord, pass through the superior cervical ganglion, and terminate via a beta-noradrenergic-junction on the pineal; for this reason, beta-blockers inhibit melatonin secretion.

Although the timing signal provided by the SCN is necessary, it is not sufficient; secretion also requires darkness. Light intensity greater than about 50 lux can cause some inhibition of melatonin secretion, and light brighter than 2000 lux completely suppresses it. Thus, in nature, the long days and short nights of summer will truncate melatonin secretion even though the SCN signal is "on" for 12 h. As a measure of day-length (and thereby season of the year), the duration of melatonin secretion is an important regulator of reproductive physiology and behavior in many seasonal breeding mammals.

To summarize, the circadian clock regulates the timing of melatonin secretion, but because light inhibits it, the environment must be dark for secretion to occur; in other words, darkness has a permissive role for melatonin secretion. The approximately 12-h duration of the SCN "on signal" for melatonin secretion (even if light is inhibiting its active secretion) can be considered an operational definition of the biological night. After jet travel, before adaptation to local time occurs, the SCN generated nocturnal signal will be synchronized to nighttime at home; thus, placement of an un-adapted jet traveler in a dimly lit room during the day may well result in melatonin secretion.

In 1983, Redman et al.<sup>20</sup> demonstrated that melatonin administration could entrain rats who had free-running rhythms when temporally isolated and maintained in constant dim light. Subsequently Lewy et al.<sup>21</sup> showed that melatonin could shift circadian rhythms in humans in a phase dependent manner. For normally entrained individuals, melatonin administration in the morning shifts rhythms later while melatonin administration in the evening shifts rhythms earlier (see Fig 2). Thus, melatonin can be thought of as a "darkness signal" since the effects are opposite to light. When phase shifting effects are plotted, the melatonin PRC is about 180 degrees out of phase with the light PRC.<sup>22</sup>

A range of melatonin doses has been tested for phase shifting and the threshold for an effect appears to be at physiological blood levels (at about 50 pg/mL). However, the dose-response curve appears to be rather flat; that is, higher doses are not much more potent than lower doses. The timing of melatonin administration (considering the melatonin PRC) is probably more important than dose. In one report, a low dose of melatonin (0.5 mg per day) was able to normally entrain a blind individual who had failed to entrain to higher doses, up to 20 mg. The authors concluded that the high dose was less effective because it was active on both the advance and delay portions of the melatonin PRC, and consequently the phase shifting effects were canceled out.<sup>23</sup>

When light exposure is combined with melatonin administration timed to produce a phase shift in the same direction, the effects are somewhat synergistic. Furthermore, if the one treatment is timed to produce a delay and the other an advance, they can be antagonistic. For example, the combination of evening melatonin (5 mg) and evening bright light (5000 lux) resulted in no phase shift; apparently, the phase advancing effect of melatonin canceled out the phase delaying effect of evening light exposure.<sup>24</sup> There are melatonin receptors in the SCN, so there is a potential feedback pathway in which circulating melatonin can influence the timing of its own secretion. Activation of these

receptors is presumably the mechanism that underlies the phase shifting effect of melatonin and its benefits for JLD, but melatonin has some direct sleep-promoting effect that may involve other mechanisms of action.

## Treatment of jet lag

Given that jet lags involves a mismatch between the endogenous circadian rhythm and the desired (or required) time for sleep, there are three conceptually different treatment strategies that can be adopted to counteract it: (1) "resetting the body clock" to a more favorable alignment. Timed light exposure and melatonin administration are the two strategies that can be used to promote phase shifting and resynchronization (re-entrainment), (2) prescribed sleep scheduling, that aims to minimize the consequences of circadian misalignment, and (3) pharmacotherapy to counteract the cardinal symptoms generated by circadian misalignment; namely, stimulant medication to counteract daytime sleepiness, and/or hypnotic medication to counteract insomnia. The three strategies will be elaborated in the remainder of the paper.

## Circadian phase-shifting

Circadian rhythms are quite stable from day to day; in other words the circadian system has substantial inertia. Although large "phase jumps" can be accomplished in highly controlled laboratory settings, under natural conditions, maximal rates of phase shifting are probably about an hour or two per day. Phase shifting treatment strategies can accelerate the resetting process, but need to be applied daily for a sustained period of several days in order to produce results.

### Timed light exposure

As light is the primary time cue for entrainment of circadian rhythms, the amount and timing of light exposure upon arrival at a new destination will be the primary factor in determining the speed and direction of re-entrainment. In most cases, exposure to natural daylight at the destination would be expected to facilitate circadian adaptation to local time; however, light exposure will vary depending on the time of travel, the season of the year, and the activity of the traveler.

Artificial light sources can be used to supplement natural daylight; however, carrying a "light box" is unwieldy for travelers. In an attempt to find a more acceptable treatment, light sources mounted on goggles were used in one study. Subjects were exposed to either three hours of bright light (3000 lux) or dim red light (10 lux) at 19:00 local time for two evenings following a westward flight from Zurich to New York.<sup>25</sup> A modestly greater phase delay (1 h) in the salivary DLMO was seen in the bright light group ( $P < 0.02$ ).

Bright light exposure has been tested as a way to realign rhythms in anticipation of jet travel. In a laboratory-based study, subject's sleep schedules were shifted 1 h earlier per day for three days as if they were going to jet travel in an eastward direction (they did not actually take a trip).<sup>26</sup> Each morning upon awakening, one group ( $N = 8$ ) was

exposed to 3.5 h of bright continuous light (>3000 lux) and another ( $N = 11$ ) to intermittent bright light (>3000 lux for 0.5 h alternating with 0.5 h off). A control group ( $N = 9$ ) was maintained in "ordinary" dim indoor light (about 60 lux). After the three days of treatment, the DLMO was shifted (on average) 2.1 h earlier with continuous bright light, 1.5 h earlier with intermittent bright light, and 0.6 h earlier with dim light.

Wearing very dark glasses to prevent unwanted light-induced phase shifts would be simpler than using artificial light sources. Light avoidance has been proven effective in several simulated shiftwork studies.<sup>27,28</sup> Daan and Lewy<sup>29</sup> pointed out that travel at or beyond about eight time zones could result in light hitting on the "wrong" portion of the light PRC; that is, promoting a phase advance when a phase delay is desired (or *vice versa*). To minimize this problem, they suggest avoiding bright light by staying indoors for the first few hours in the morning after long eastward flights, and few hours in the evening after long westward flights. If going outdoors during these hours, wearing low transmittance sunglasses or goggles may help to reduced the risk. After a few days, the light PRC will presumably have shifted enough so that light avoidance can be discontinued.

Questions have been raised about the safety of artificial bright light exposure for humans, especially the possibility of phototoxic effects on the lens and/or the retina. In order to mimic sunlight, some early light therapy devices used "full spectrum" light sources that included UV radiation. However, UV wavelengths are unnecessary for the phase shifting effect of light and should be avoided.<sup>30</sup> If full spectrum tubes are installed, a diffuser panel placed over the light source effectively filters UV radiation. Because most light sources used for treatment are no brighter than ordinary sunlight, they would seem *a priori* to be as safe. However, caution is in order for patients with ocular pathology (e.g., lenticular cataracts or retinal degeneration).

#### Timed melatonin administration

Melatonin administration is the most studied treatment for jet lag and the evidence is quite compelling that it can accelerate adaptation to a new time zone. In various studies it has been administered in doses ranging from 0.5 to 10 mg. It has been given at local bedtime, for up to 3 days prior to departure and up to 5 days upon arrival at the destination. A variety of outcome measures have been employed in these trials including subjective ratings scales of jet lag symptoms, sleep logs, and standardized mood scales, as well as (in a few cases) objective measures of sleep (polysomnography and sleep latency testing).<sup>31,32</sup> Circadian phase has been measured in a few studies, but the phase markers used, namely cortisol<sup>33</sup> and oral temperature<sup>31</sup> were probably distorted by masking influences. Field studies utilizing current phase marker technology, for example, measurement of the DLMO, would be welcomed. Most studies have tested melatonin for eastward flight in which taking melatonin at bedtime could have both soporific and phase-resetting benefits. According to the melatonin PRC, if taken at local bedtime after westward flight, it could inhibit phase resetting. However, in two randomized, controlled trials, benefits of melatonin administration on jet lag scores and sleep were seen

even when administered at bedtime after westward travel, albeit over 12 time zones or more.<sup>34,35</sup>

The optimal dose remains to be determined, but larger doses probably have more hypnotic activity than lower doses that may (in theory) have a greater phase shifting effect. In a dose comparison study, 5 mg immediate-release melatonin was found to be more effective than a 2 mg slow-release formulation, though only slightly more effective than a 0.5 mg immediate-release formulation.<sup>36</sup> Melatonin failed to add benefit when it was used in combination with the hypnotic drug zolpidem.<sup>37</sup> In the few studies that monitored melatonin treatment for potential side effects, there were no differences from placebo.

#### Hypnotic medications

To reiterate, jet lag induced insomnia is primarily caused by a mismatch between the circadian alerting process and the sleep schedule at the destination. Also, exogenous factors such as a novel (often uncomfortable) bed and bedroom, ambient light, and noise can interfere with restful sleep upon arrival. Jet lag related insomnia could be expected to remit when either the traveler adapts to a new locale or returns home; thus a short course of hypnotic medication to treat travel-related insomnia can be readily justified.

Benzodiazepine (as well as non-benzodiazepine) hypnotic medications have been demonstrated to be effective for jet lag induced insomnia in a number of field trials.<sup>37-45</sup> For example, in a large ( $N = 133$ ) randomized placebo-controlled trial, zolpidem 10 mg at bedtime for 3-4 nights following eastward travel across 5-9 time zones was found to significantly improve total sleep time and sleep quality while reducing awakenings from sleep.<sup>42</sup> However, no objective measures of sleep were assessed; only self-reports.

Several studies have compared hypnotics to melatonin. For example, zopiclone (5 mg) was compared to melatonin (2 mg) or placebo administered for one night, after arrival, in 30 subjects traveling eastward across 5 time zones.<sup>43</sup> The subjects repeated the trip three times, so that each subject served as his/her own control. Zopiclone and melatonin were found to be equally effective at improving sleep duration and quality as compared to placebo.

Although usually safe, adverse effects of hypnotic agents for jet lag have been reported. For example, triazolam was implicated in several dramatic cases of global amnesia following its use to promote sleep during jet travel.<sup>46</sup>

Sleeping medicines promote sleep and reduce insomnia whatever the etiology, so it is not surprising they are helpful for jet lag-induced insomnia. It is less well established that treatment improves daytime alertness. Although improving sleep will reduce homeostatic sleep drive, until the circadian clock has been reset to local time, the circadian alerting process will be out of phase with time awake, and thus daytime sleepiness is quite possible even if prior sleep duration has been extended with hypnotic medication.

#### Promoting alertness with stimulant medication

There are two ways that the symptom of excessive sleepiness related to circadian misalignment can be explained: (1) persistent, foreshortened or inefficient sleep causes a build up of homeostatic sleep drive (debt). (2) the

circadian alerting signal is not “on” when the person wants to be awake. As mentioned earlier, many other factors can add to travel-induced sleep disruption and consequent sleepiness.

The first countermeasure many travelers use to combat sleepiness is increased coffee consumption. This strategy has been tested in two double-blind controlled field trials of slow-release caffeine (SRC) evaluated for its effects on alertness and other jet lag symptoms. In the two studies involving eastward flight over seven time zones,<sup>31,33</sup> placebo was compared to SRC 300 mg and melatonin 5 mg taken daily for five days starting on the day of travel to 3 days post-flight ( $N = 9$  for each group). Entrainment, as measured by salivary cortisol levels, was complete in five days for the treated groups, but took nine days for the placebo group. Subjects treated with SRC were less sleepy by objective measures than with either melatonin or placebo (no significant difference in subjective sleepiness) but took longer to get to sleep and had more awakenings at night.

Modafinil, a drug developed for the treatment of narcolepsy, has been shown to improve alertness in phase shifting experiments that simulate jet lag, but there have been no field studies to date.

### Strategic sleep scheduling

One of the simplest ways to avoid jet lag may be to maintain a home-based sleep–wake schedule after arrival at the destination. This would seem particularly appropriate for trips of short duration. Perhaps because this strategy has such strong face validity, it has not been subjected to much formal investigation. However, there is one field study (employing a balanced, crossover design) that compared maintaining a home-based schedule to a destination-congruent schedule during a two-day layover after a nine-hour westward flight.<sup>47</sup> When subjects kept the home-based sleep schedule, they had longer and better quality sleep, experienced less wake-time sleepiness, and had lower global jet lag ratings. Despite their improved sleep and alertness, one third of the subjects expressed a preference for adopting the destination sleep schedule in order to enjoy local social activities and eating schedules.

Another approach may be to adjust one’s sleep schedule (along with circadian rhythms) in the days preceding travel to more closely match the destination schedule. Again, this approach has strong face validity, but has not had much formal testing. As mentioned above, advancing the timing of sleep for three days, combined with bright light exposure upon awakening, was shown to phase shift rhythms in anticipation of eastward travel.<sup>26</sup> No studies have been performed using this approach for westward travel in which it would be logical to delay the timing of sleep combined with evening bright light exposure.

Travelers are often frantically busy preceding major trips and may sleep-deprive themselves as they try to complete pressing tasks before they leave home; this may be an important predisposing factor in jet lag. Simply getting sufficient sleep prior to traveling will minimize the residual sleep debt. First-class accommodations during

travel that allow a reclining posture during flight probably alleviate much of the sleep deprivation associated with long distant jet travel, but there have been no studies of the benefits.

### Summary and conclusions

A rational approach to the treatment of jet lag disorder can be grounded on an understanding of the underlying pathophysiology of circadian misalignment that undermines sleep and alertness. After jet travel across time zones, appropriately timed light exposure and/or melatonin administration can facilitate resynchronization of the circadian clock to local conditions. Circadian science has provided the scientific foundation for treatment interventions, but specific treatment protocols need to be tested and refined with well-conducted field trials.

### Conflict of interest

None.

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