



EDUCATIONAL OBJECTIVE: Readers will suggest strategies to lessen jet lag and shift work disorders

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Jet lag and shift work sleep disorders: How to help reset the internal clock

ABSTRACT

Jet lag sleep disorder and shift work sleep disorder are the result of dyssynchrony between the internal clock and the external light-dark cycle, brought on by rapid travel across time zones or by working a nonstandard schedule. Symptoms can be minimized by optimizing the sleep environment, by strategic avoidance of and exposure to light, and also with drug and behavioral therapies.

KEY POINTS

Symptoms include daytime anergia, alternating complaints of insomnia and hypersomnia, emotional disturbances, and gastrointestinal distress. The severity depends on the degree and the duration of dyssynchrony, as well as on innate factors such as age and whether the patient is an “early bird” or a “night owl.”

Drug treatment addresses sleep-related symptoms (eg, somnolence, insomnia) and attempts to hasten circadian reacclimation.

Exposure to bright light in the hours leading up to the patient’s minimum core body temperature tends to push the internal clock later in time, whereas bright light in the hours immediately afterward pushes the clock earlier in time.

FOR PEOPLE WHO MUST TRAVEL long distances east or west by air or who must work the night shift, some relief is possible for the grogginess and disorientation that often ensue. The problems arise from the body’s internal clock being out of sync with the sun. Part of the solution involves helping reset the internal clock, or sometimes, preventing it from resetting itself.

This review will focus on jet lag sleep disorder and shift work sleep disorder, with an emphasis on the causes, the clinical assessment, and evidence-based treatment options.

WHEN THE INTERNAL CLOCK IS OUT OF SYNC WITH THE SUN

Circadian rhythm sleep disorders are the result of dyssynchrony between the body’s internal clock and the external 24-hour light-dark cycle. Patients typically present with insomnia or excessive somnolence. These disorders may represent an intrinsic disorder, such as delayed or advanced sleep-phase disorder, or may be the result of transmeridian air travel or working nonstandard shifts.¹

Sleep and wakefulness are conceptually governed by two processes, “process S” and “process C.”² The homeostatic drive to sleep (process S) is proportional to the duration of sleep restriction, and it becomes maximal at about 40 hours.³ In contrast, process C creates a drive for wakefulness that variably opposes process S and depends on circadian rhythms intrinsic to the organism (FIGURE 1).⁴ Coordinating this sleep-wake rhythm (and numerous other behavioral and physiologic processes) are the neurons of the suprachiasmatic nuclei of the hypothalamus.^{5–8}

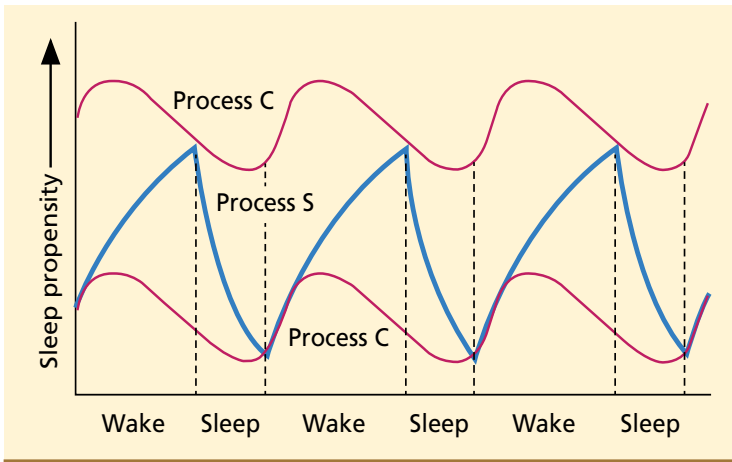


FIGURE 1. The two-process model of sleep regulation. Sleep propensity grows during periods of wakefulness and abates during sleeping periods. The homeostatic process (process S, blue line) is limited to a range of values determined by a clock-like circadian process (process C, red lines) that varies with the biological time of day.

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The intrinsic circadian cycle is slightly longer than 24 hours

The intrinsic human circadian period is typically slightly longer than 24 hours,⁹ but it is synchronized (“entrained”) to the 24-hour day by various environmental inputs, or *zeitgebers* (German for “time-givers”), the most important of which is light exposure.¹⁰

When the internal clock is out of sync with the sun, the misalignment can result in daytime anergia, alternating complaints of insomnia and hypersomnia, and various other symptoms, including emotional disturbances and gastrointestinal distress. In particular, long-distance air travel or a nocturnal work schedule overwhelms the ability of the intrinsic clock to adjust rapidly enough, and the result is jet lag sleep disorder or shift work sleep disorder.¹

■ TOOLS TO EVALUATE CIRCADIAN RHYTHM DISTURBANCES

A thorough history is the cornerstone of the evaluation for all sleep disorders, and if a circadian rhythm disturbance is suspected, the sleep history is supplemented with specific questions to establish a clear diagnosis.

When assessing for jet lag disorder, ask about:

- The patient’s degree of sleep deprivation before and during travel

- His or her innate circadian preference (ie, whether he or she is a “night owl” or “early bird”)
- Patterns of alcohol and caffeine consumption.

When assessing for shift work disorder, include the above questions and also look for differences in the sleep-wake schedule on working days vs nonworking days, as well as external contributors to poor sleep quality (eg, the degree to which daytime sleep is not “protected”).

The following tools help in acquiring this information.

Sleep diary

In a sleep diary or log, patients record the times that they take naps, maintain consolidated sleep, and subsequently arise. The diary also prompts the patient for information about sleep latency, wakefulness after sleep onset, time in bed, medication and caffeine intake, and the restorative quality of sleep.

While the sleep diary by itself may provide insight into counteractive sleep-related behaviors and misperceptions the patient may have, compliance is often limited. Therefore, the sleep diary is best used in conjunction with actigraphy.

Actigraphy

An actigraph is a wristwatch-size motion detector, typically worn continuously for 7 days or longer. The data it gathers and stores serve as a surrogate measure of various sleep-wake variables.¹¹

Either a sleep diary or actigraphy is required to demonstrate the stability of sleep patterns and circadian preference, but the actigraph typically generates more reliable data.^{11,12} It is also valuable in assessing the response to treatment of circadian rhythm sleep disorders.¹³

Are you an early bird or a night owl?

The Morningness-Eveningness questionnaire contains 19 items. Night owls tend to score lower on it than early birds do.¹⁴ This information may help some people avoid situations in which they may not do well, such as an early bird going on a permanent night-shift schedule.

Other assessment tools

Polysomnography is used primarily to rule out sleep-disordered breathing; it is not indicated for routine evaluation of circadian rhythm sleep disorders.

The minimum core body temperature and the peak melatonin secretion follow a 24-hour cycle. Although these measures are often used in research, they are not routinely used in clinical practice. (The minimum core body temperature is discussed further below.)

JET LAG SLEEP DISORDER

Jet lag results from air travel across multiple time zones, with a resultant discordance between the internal circadian clock and the destination's light-dark cycle. Most sufferers report sleeping poorly at night and feeling groggy during the day, and some also experience general malaise and gastrointestinal distress.¹

The severity depends on a number of variables.

Going west is easier than going east

Westward travel is normally less taxing than eastward travel, as it requires setting one's internal clock later rather than earlier. Presumably, because the circadian period tends to exceed 24 hours, we can move our internal clock later by about 2 hours per day, but we can move it earlier by only 1 to 1.5 hours.^{15,16}

The more time zones crossed, the longer it takes the circadian pacemaker to re-entrain and the longer-lasting and more severe are the symptoms of jet lag. Travel across one or two time zones is only transiently troublesome.

Does age affect jet lag?

Whether age affects the severity of jet lag is not yet known.

In a study of simulated jet lag (requiring a 6-hour advance), middle-aged people (ages 37 to 52) experienced a greater degree of fragmented sleep on polysomnography than younger ones (ages 18 to 25). The older group also had greater impairment in daytime alertness, suggesting that phase tolerance—ie, the ability to sleep at an abnormal time in the circadian cycle¹⁷—decreases with age. However,

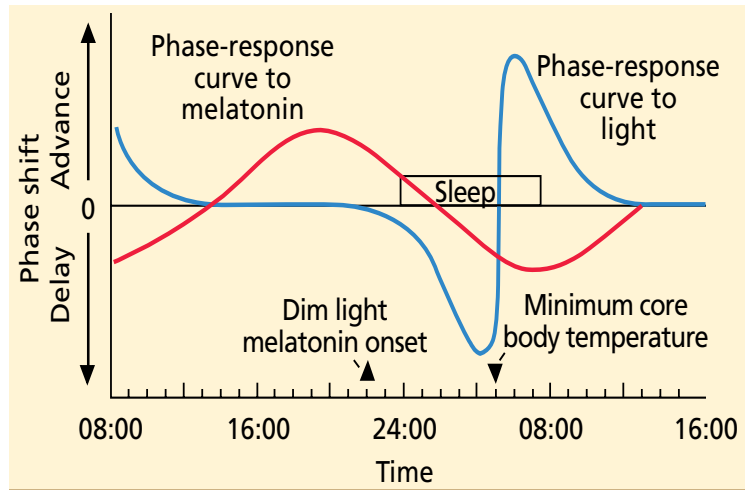


FIGURE 2. A schematic human phase-response curve to light (blue line) and a one to exogenous melatonin (red line). The y axis shows the direction and relative magnitude of the phase shift produced by the administration of light or melatonin at various times, which are shown on the x axis. This graph shows typical times and phase relationships among these rhythms when the circadian clock is entrained to a 24-hour day. For individuals with earlier or later circadian rhythms, the local time axis should be adjusted accordingly. The light phase-response curve is a schematic based on the results of numerous studies. The melatonin curve is based on a single study using 0.5-mg doses of melatonin.²²

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two field studies involving both eastward and westward travel yielded the opposite results, suggesting that older age may actually protect against jet lag.¹⁸⁻²⁰

Methodologic differences preclude direct comparisons of the studies, as do differences in the age groups studied.

Light exposure can help or hurt, depending on the timing

Light exposure is of primary importance in shifting the circadian clock, and the direction of the shift depends on the timing of the exposure (FIGURE 2).²⁰⁻²²

Our core body temperature dips to its lowest point about 2 to 3 hours before we habitually awake. Exposure to bright light in the hours leading up to this minimum (the inverted triangle in FIGURE 2) sets our internal clock later (a phase delay)—desirable, say, for someone travelling from New York City to Los Angeles. Conversely, exposure to bright light

Jet lag plan for seven time zones east

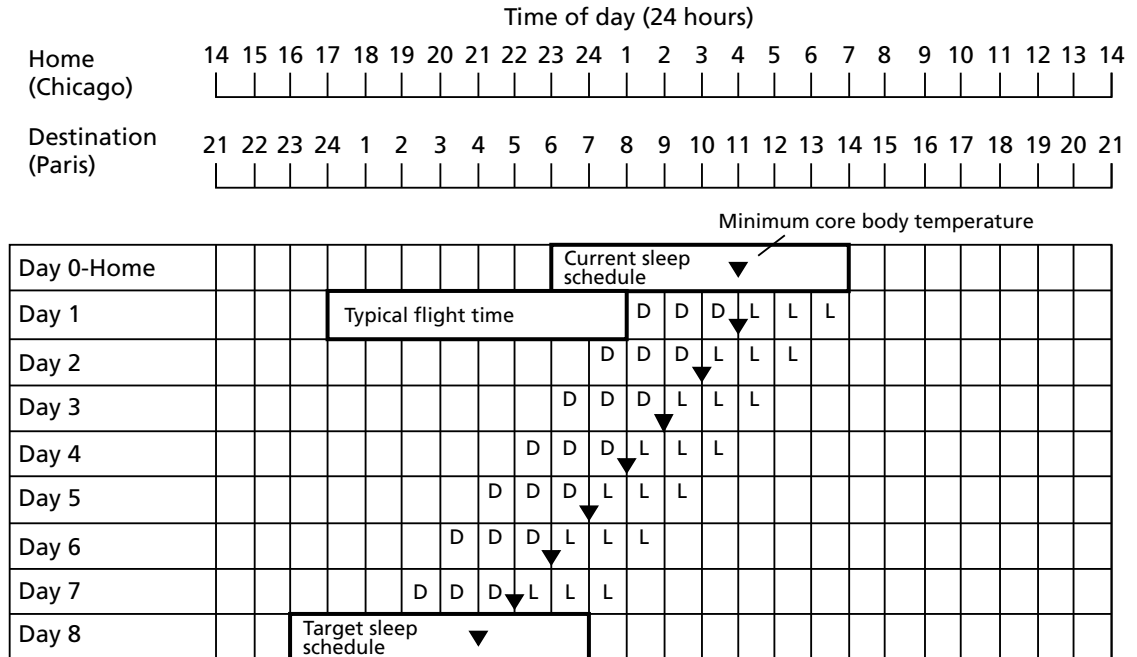


FIGURE 3. Diagram demonstrating a flight from Chicago to Paris, seven time zones east. Times when darkness and light should be sought are denoted by the letters “D” for darkness and “L” for light. The inverted triangles represent the minimum core body temperature. Subsequent to arrival, the depicted light-dark pattern should result in average daily phase shifts of 1 hour.

BURGESS HJ, EASTMAN CT. PREVENTION OF JET LAG. AMERICAN COLLEGE OF PHYSICIANS, 2010. [HTTP://PIER.ACPCONLINE.ORG/PHYSICIANS/SCREENING/ PREV1015/PREV1015.HTML](http://pier.acponline.org/physicians/screening/prev1015/prev1015.html). MODIFIED WITH PERMISSION OF THE AMERICAN COLLEGE OF PHYSICIANS.

Westward travel is normally less taxing than eastward travel

after this temperature minimum sets the clock earlier.

Inadvertent shifting of circadian phase in the wrong direction (“antidromic re-entrainment”) is common and delays circadian reacclimation and the dissipation of jet lag symptoms.

For example (FIGURE 3),²³ a typical flight from Chicago to Paris (seven time zones to the east) arrives there early in the morning Paris time. Although the clocks at Charles de Gaulle airport say 08:00, the traveler’s internal clock says it is still 01:00. Furthermore, his or her core body temperature will reach its minimum at about 04:00 Chicago time, or 11:00 Paris time. If the traveller decides to go for a walk right away, the light exposure will promote a phase delay rather than the desired phase advance. Therefore, circadian re-entrainment will be relatively prolonged.²⁴

We discuss ways to reduce antidromic re-entrainment in more detail further below.

Other factors

Other factors that contribute to travel fatigue include sleep deprivation (before the flight or en route), acute discomfort as the plane ascends to its cruising altitude,²⁵ and excessive alcohol or caffeine intake during the flight. Although the effects of these factors rapidly diminish once one reaches the travel destination, jet lag will persist until circadian re-entrainment occurs.¹⁵

NONDRUG THERAPIES FOR JET LAG SLEEP DISORDER

The goal of treatment is to realign the circadian rhythm in the most rapid and efficient way and to minimize symptoms in the meantime. Frequent shifts to different time zones, often required in business travel, are very difficult to accommodate, and business travelers actually may do better if they remain on their home-based schedule.

Jet lag plan for nine time zones east

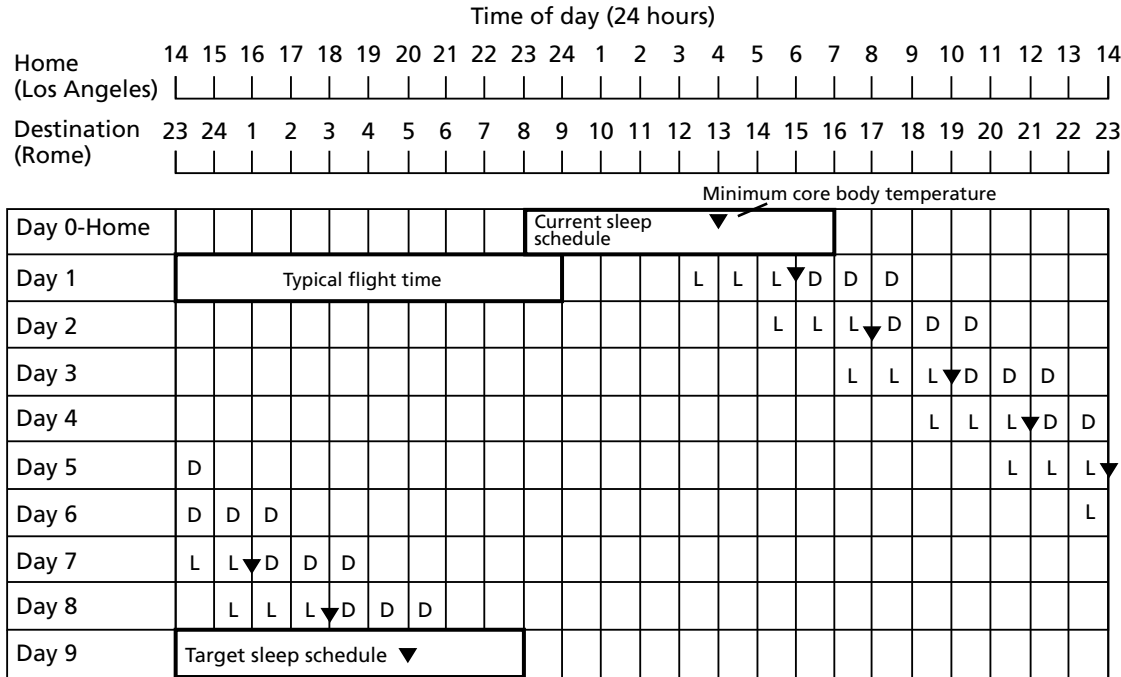


FIGURE 4. The diagram demonstrates a flight from Los Angeles to Rome, nine time zones east. Times when darkness (letter D) and light (letter L) should be sought are also indicated. The inverted triangles represent the minimum core body temperature. The depicted light-dark pattern should result in average daily phase shifts of 2 hours.

BURGESS HJ, EASTMAN CT. PREVENTION OF JET LAG. AMERICAN COLLEGE OF PHYSICIANS, 2010. [HTTP://PIER.ACPONLINE.ORG/PHYSICIANS/SCREENING/PREV1015/PREV1015.HTML](http://pier.acponline.org/physicians/screening/prev1015/prev1015.html). USED WITH PERMISSION OF THE AMERICAN COLLEGE OF PHYSICIANS.

Inadvertent shifting of circadian rhythm in the wrong direction is common

One study compared keeping home-based sleep hours as opposed to adopting local sleep hours during a 2-day stay after a 9-hour westward flight.²⁶ Travelers who remained on home-based hours were less sleepy and had lower (ie, better) global jet lag ratings than those who adopted local sleep hours, in part because of better sleep quality and duration. Nevertheless, about one-third of the participants said they preferred to adhere to the local schedule.

Strategic avoidance of, and exposure to, light

If the traveler intends to remain at the destination long enough, he or she can adjust better (and avoid an antidromic process) via strategic avoidance of and exposure to light.²⁴

Burgess and Eastman^{23,27} have devised plans to help in deciding whether a phase delay or phase advance is most desirable, de-

pending on the number of time zones crossed. Generally, shifts earlier in time are required for eastward flights (as in FIGURE 3), and shifts later in time are required for westward flights. However, advances of 8 hours or more are more readily accomplished by a phase delay (FIGURE 4).^{23,28}

People travelling east, who want to set their clocks ahead (a phase advance), need to keep to the dark in the 3 hours leading up to the time they reach their minimum core body temperature (depicted as “D” in FIGURE 3), and then expose themselves to light in the 3 hours immediately after (“L” in FIGURE 3). Thus, the traveler from Chicago to Paris would do better by avoiding light exposure on arrival, either by remaining in darkness in his or her hotel room, or by wearing dark sunglasses when outdoors. Wearing sunglasses during transit to the hotel would also help avoid light exposure.

When attempting to delay circadian rhythms, the opposite light-dark patterns are

sought, as depicted in **FIGURE 4**. As flight and layover patterns often do not permit strict adherence to these measures, they represent idealized scenarios.

The first step is to make a grid with a concurrent listing of home and destination times. In the example in **FIGURE 3**, the person is traveling seven time zones east. On day 0, a rectangle is drawn around the times representing home-based sleep hours.

Next, we mark the time at which we expect the traveler's core body temperature to reach its minimum (inverted triangle). If the person habitually sleeps no more than 7 hours per night, then we mark this point as 2 hours before his or her habitual wake-up time; if the person sleeps more than 7 hours, then we place it 3 hours before wake-up time.^{23,29} This process is repeated at the bottom of the grid to represent the desired sleep schedule at the traveler's destination. The distance between the home and the destination-based minimum core body temperature symbols represents the required degree of circadian realignment.

If a phase advance is required (eg, if travelling from Chicago to Paris), the core body temperature symbol is drawn on day 1 in the same location as day 0. For each subsequent day, the symbol is moved 1 hour earlier (which is about how fast the internal clock can advance),^{15,27} until a clock time within 1 hour of the desired destination core body temperature time is reached or satisfactory sleep and daytime functioning are achieved (**FIGURE 3**). If a phase delay is required (eg, if travelling from New York City to Los Angeles), the symbol is drawn 2 hours later on day 1 than on day 0 (reflecting the greater ease at which delays are achieved),^{15,27} with subsequent daily shifts in 2-hour increments, again until a clock time within 1 hour of the desired destination minimum core body temperature time is reached or satisfactory sleep and daytime functioning are achieved.

Requirements for darkness can be met with protective eyewear (ie, dark sunglasses), or by remaining in a dark room. Light requirements can be met with outdoor exposure, with a commercial light box, or with a separate apparatus (eg, goggles, visors) portable enough for travel.

■ DRUGS TO TREAT JET LAG SLEEP DISORDER

Melatonin appears safe

Most field studies have found that nightly doses of melatonin (2–8 mg) improve the quality of sleep^{30–32} or alleviate daytime symptoms of jet lag, or both.^{20,30,31,33–36} Immediate-release preparations appear to be more effective than slow-release ones.³¹ Although most studies looked exclusively at adaptation to eastward travel,^{30–32,35,36} one studied westward travel,³³ and another assessed melatonin's effects during both departure and return trips that traversed 11 time zones.³⁴

In studies of preflight dosing, melatonin was scheduled for up to 3 days before departure (and en route in two instances),^{30,34} at clock hours corresponding to the nocturnal sleep period at the travel destination (consistent times daily), and then for a subsequent 3 to 4 days between a destination time of 22:00 and 00:00 hours (ie, at bedtime).^{30,31,34–36} Several other studies further simplified this regimen, with participants taking nocturnal melatonin only on arrival at the destination, either for eastward^{31,32} or for westward travel.³³

The study involving solely westward travel (Los Angeles to New Zealand) was the only one of the studies with positive findings that allowed for comparisons between participants who received melatonin before departure (3 days at 5-mg doses, taken between 07:00 and 08:00 Los Angeles time) and continuing for 5 days after arrival at 22:00 to 00:00 New Zealand time, and those who received melatonin beginning only on arrival.³³ Significantly better jet lag outcomes were found in the latter group.

An important caveat is that melatonin is sold over the counter as a nutritional supplement and is not regulated by the United States Food and Drug Administration (FDA), so verification of purity of the product is difficult.

A comprehensive review by the National Academy of Sciences stated that, given the available data, short-term use of melatonin in total daily doses of 10 mg or less in healthy adults appears to be safe.³⁷

Benzodiazepine receptor agonists improve sleep, but maybe not sleepiness

The use of standard hypnotics during periods of circadian realignment appears to be com-

Advances of 8 hours or more are more readily accomplished by phase delay

monplace but has not been well studied.²⁰ Trials of the newer benzodiazepine receptor agonists—three studies of zolpidem (Ambien) 10 mg^{30,38,39} and two of zopiclone 5 to 7.5 mg^{32,40}—found consistently favorable subjective^{30,38} and objective^{32,39,40} outcomes in counteracting jet-lag-induced insomnia (for both eastward and westward travel). (Note: Zopiclone is not available in the United States, but its enantiomer eszopiclone [Lunesta] is.) However, the evidence is less clear for daytime symptoms of jet lag, with outcomes reported as favorable,³⁰ equivocal,⁴⁰ or inaccessible.^{32,38,39}

The discrepancy between studies incorporating systematic daytime assessments may be due to differential medication effects (zolpidem vs zopiclone).

In two studies that compared these standard hypnotics to oral melatonin, one found that zopiclone 5 mg and melatonin 2 mg were equally beneficial with respect to sleep variables (other jet lag symptoms were not assessed).³² In another study, zolpidem 10 mg was superior to melatonin 5 mg for sleep and other jet lag symptoms, and the combination of zolpidem and melatonin was no better than zolpidem alone.³⁰

Importantly, however, adverse effects were more frequent in those taking zolpidem and included nausea, vomiting, and confusion.³⁰ Although these effects were not deemed serious, 14 participants (10%) withdrew from the study.

Stimulants

Caffeine is commonly used to combat the sleepiness of jet lag, but only two controlled field studies have assessed its efficacy.^{41,42} Both used slow-release preparations at a daily dosage of 300 mg.

In one study, after an eastward flight traversing seven time zones, participants took the pill at 08:00 destination time every day for 5 days.⁴¹ Curiously, alertness and other jet lag symptoms were not assessed, but circadian rhythms (determined by levels of cortisol in saliva) were re-entrained at a more rapid rate with caffeine than with placebo, and to a degree comparable with that achieved by exogenous melatonin.

In a follow-up study by the same group, those receiving caffeine were objectively less sleepy (as assessed by multiple sleep latency

tests) than those taking melatonin or placebo, but subjective differences between groups were not identified.⁴² Furthermore, those taking caffeine had significantly more nocturnal sleep complaints, as assessed both objectively and subjectively.

A recent randomized, double-blind, placebo-controlled trial of the stimulant armodafinil (Nuvigil) found less sleepiness on multiple sleep latency testing and a decrease in jet leg symptoms with a dosage of 150 mg than with placebo.⁴³

SHIFT WORK SLEEP DISORDER: DEFINITION, PREDISPOSING FACTORS

Shift work refers to nonstandard work schedules, including on-call duty, rotating shifts, and permanent night work. In the United States, one in five workers works a nonstandard shift.²⁰

While shift work presents obvious difficulties, the diagnosis of shift work sleep disorder is reserved for those who have chronic insomnia or sleepiness at times that are not conducive to the externally demanded sleep-wake schedule, despite having the opportunity for sufficient daytime sleep.¹ When defined in such a fashion, this disorder may afflict nearly a third of workers,⁴⁴ with potential adverse effects on safety, health, and quality of life.

Older age is considered a risk factor for intolerance to shift work.²⁰ In a study of physiologic phase shifts in response to night work, older workers were less able to recover after several night shifts.⁴⁵ A large survey of police officers working the night shift supported the finding of more sleep disruption and on-duty sleepiness in older people.⁴⁶

TREATMENT OF SHIFT WORK SLEEP DISORDER

Bright light at work, sunglasses on the way home

Various field studies have described hastening of circadian adaptation (and immediate alerting effects) during night shifts with the use of bright light.²⁰

Boivin and James⁴⁷ found that workers who received 6 hours of intermittent bright light during their shifts experienced significantly

Melatonin is sold as a nutritional supplement, which is not inspected for purity

greater phase delays than those who received no such intervention. Those receiving bright light also wore sunglasses during the commute home (to protect from an undesired phase advance), and this has demonstrated favorable effects as an independent intervention.⁴⁸

Drug treatment of shift work sleep disorder

Melatonin: Mixed results. Two field studies found that taking melatonin (5–6 mg) before the daytime sleep period had a favorable impact on subjective sleep quality.^{49,50} However, two other studies found no such benefit with doses ranging from 6 to 10 mg.^{51,52} Differences between these studies—eg, shift schedules, dosages, and the time the melatonin was taken—preclude definitive comparisons.

Effects of melatonin on workplace alertness are indeterminate because of inconsistent measurements of this variable. Importantly, a simulated shift work study found no phase-shifting advantages of melatonin in those who concomitantly used bright light during their work shift with or without morning protective eyewear.⁴⁸

Hypnotic drugs. In simulation studies and field studies, people taking benzodiazepine receptor agonists have consistently said they sleep better.^{53–58} A simulation study noted additional benefit in the ability to stay alert during the night shift (assessed by maintenance of wakefulness testing),⁵⁵ but two other studies saw no changes in manifest sleepiness (assessed with multiple sleep latency tests).^{53,54} These divergent findings may represent different effects on these two dimensions of sleepiness.

The only field study to assess post-sleep psychomotor performance found no impairments after taking 7.5 mg of zopiclone, a relatively long-acting nonbenzodiazepine hypnotic.⁵⁷

Stimulants. In the largest trial to date of shift work sleep disorder, modafinil 200 mg (the only drug currently FDA-approved for shift work sleep disorder) had significant benefits compared with placebo with respect to objective measurements of workplace sleepiness, reaction time performance testing, and self-rated improvement of symptoms.⁵⁹ Perhaps because of the low dose studied, both treated and untreated patients continued to

manifest sleepiness within the pathologic range on objective testing.

Although the efficacy of caffeine is well documented as a countermeasure for sleepiness during experimentally induced sleep deprivation,²⁰ very few field trials have specifically addressed impairments associated with shift work sleep disorder. In one study, caffeine at a dose of 4 mg/kg taken 30 minutes before starting a night shift provided objective improvement in both performance and alertness.⁶⁰

Strategic napping is an additional practical intervention to promote alertness during night shifts, and cumulative data indicate that it provides objective and subjective improvements in alertness and performance.^{61,62} Earlier timed naps (ie, before or during the early portion of a shift) of short duration (ie, 20 minutes or less) are likely to produce maximal benefit, because they avoid sleep inertia (the grogginess or sleepiness that may follow a long nap), and also because they have no effect on the subsequent daytime sleep bout.^{61,63}

Interventions may also be used in combination. For example, napping in conjunction with caffeine results in a greater degree of increased objective alertness than either intervention alone.⁶⁰

How about days off?

The recommendations described here presume that shift workers maintain the workday sleep-wake schedule continuously, including when they are not at work. This is likely not a real-world scenario.

Smith et al⁶⁴ developed a “compromise” phase position, whereby internal rhythms are optimized to facilitate alertness during work and sleepiness during the day, while allowing one to adopt a non-workday sleep schedule that maintains accessibility to family and social activities. In brief, non-workday sleep starts about 5.5 hours earlier than workday sleep; all sleep bouts are followed by brief exposure to bright light (to avoid excessive phase delay); and, as described previously, both workplace bright light and protection from morning light are implemented.

Although further studies are needed to determine whether this regimen is practical in real life, study participants who achieved desired partial phase shifts had performance

In the United States, one in five workers does shift work

ratings on a par with baseline levels, and comparable to those in a group that achieved complete re-entrainment.⁶⁴

Finally, all shift workers need to be encouraged to protect the daytime bedroom

environment just as daytime workers protect their nighttime environment. Sleep should be sought in an appropriately darkened and quiet environment, phones and doorbells silenced, and appointments scheduled accordingly. ■

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