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Sleep Disorders

Treatment of Shift Work Disorder and Jet Lag

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Opinion statement

With the growth of the 24-hour global marketplace, a substantial proportion of workers are engaged in nontraditional work schedules and frequent jet travel across multiple time zones. Thus, shift work disorder and jet lag are prevalent in our 24/7 society and have been associated with significant health and safety repercussions. In both disorders, treatment strategies are based on promoting good sleep hygiene, improving circadian alignment, and targeting specific symptoms.

Treatment of shift work must be tailored to the type of shift. For a night worker, circadian alignment can be achieved with bright light exposure during the shift and avoidance of bright light (with dark or amber sunglasses) toward the latter portion of the work period and during the morning commute home. If insomnia and/or excessive sleepiness are prominent complaints despite behavioral approaches and adequate opportunity for sleep, melatonin may be administered prior to the day sleep period to improve sleep, and alertness during work can be augmented by caffeine and wake-promoting agents.

For jet lag, circadian adaptation is suggested only for travel greater than 48 h, with travel east more challenging than travel west. Although advancing sleep and wake times and circadian timing for eastward travel with evening melatonin and morning bright light several days prior to departure can help avoid jet lag at the new destination, this approach may be impractical for many people, Therefore, strategies for treatment at the destination, such as avoidance of early morning light and exposure to late-morning and afternoon light alone or in conjunction with bedtime melatonin, can accelerate re-entrainment following eastward travel. For westward travel, a circadian delay can be achieved after arrival with afternoon and early-evening light with bedtime melatonin.

Good sleep hygiene practices, together with the application of circadian principles, can improve sleep quality, alertness, performance, and safety in shift workers and jet travelers. However, definitive multicenter randomized controlled clinical trials are still needed, using traditional efficacy outcomes such as sleep and performance as well as novel biomarkers of health.

Introduction

Humans have an endogenous circadian rhythm slightly longer than 24 h. The International Classification of Sleep Disorders describes nine circadian rhythm disorders defined by a persistent or recurrent pattern of sleep disturbance resulting from either alterations of the circadian timekeeping system or misalignment between the endogenous circadian rhythm and exogenous factors that affect the timing and duration of sleep [1]. Shift work disorder and jet lag are two circadian rhythm disorders that occur due to the alteration of the external environment relative to the internal circadian timing system [2].

Shift work disorder

As of 1991, 20% of the United States workforce participated in some type of shift work [3]. Of these, more than 30% of night workers and 25% of rotating shift workers meet criteria for shift work sleep disorder [3]. In Europe, only 24% of the workforce keeps conventional working hours, and 18.8% have a work schedule that involves night shift work [4]. Shift work disorder is characterized by both insomnia and excessive sleepiness associated with the work period occurring during the usual time for sleep [1]. The diagnosis requires that symptoms are of at least 1 month's duration and circadian misalignment must be demonstrated with a sleep diary or actigraphy [1]. Insomnia and excessive sleepiness are thought to be primarily due to a misalignment between the scheduled sleep/wake cycle and the circadian propensity for sleep and alertness. Typically, the patient is attempting to sleep when the circadian signal for alertness is high and working at a time when the circadian alertness levels are low [1]. In addition to circadian factors, sleep is often shortened in shift workers because of problems with the environment for sleep and because domestic and social responsibilities encroach on the worker's nonconventional sleep time [2]. Therefore, sleep loss, in addition to circadian misalignment, contributes to decreased alertness during night work [5]. Sleepiness in shift workers can be profound: one third of night workers admit to nodding off once a week during work, and one half report falling asleep while commuting [6]. In addition to sleepiness, circadian misalignments in performance have also contributed to serious accidents, including the incidents at Three Mile Island and Chernobyl and the Exxon Valdez disaster [5]. Shift workers with shift work disorder are at higher risk for cardiovascular disease, ulcers, depression, and absenteeism than shift workers without shift work disorder [5]. Because of both public safety concerns and consequences to the patient, treatment of shift work disorder is imperative.

Jet lag disorder

Jet lag disorder is defined as *symptoms* of insomnia and/or excessive daytime sleepiness resulting from travel across at least two time zones [1]. It is also associated with compromised daytime function, general malaise, or somatic complaints (eg, gastrointestinal symptoms) occurring within 1 to 2 days of travel [1]. Unlike travel fatigue, jet lag symptoms do not resolve with an adequate sleep period upon arrival and may occur even when unfavorable air travel conditions (cramped space, etc.) are minimized [7]. Because the intrinsic clock cannot adjust to the change in time zones as rapidly as we can traverse them with jet travel, there is a resultant discord between the timing of sleep as generated by the endogenous circadian rhythm and the sleep/wake times necessary in the new time zone [8••]. Eastward travel often results in sleep-onset insomnia as the endogenous circadian rhythm (as set by the location of origin) is not conducive to sleep at the new, earlier time at the destination; the circadian rhythm must advance. In westward travel, difficulties in remaining asleep are a more prominent problem, as the circadian alerting signal occurs during the desired sleep period at the new destination; the circadian rhythm must delay [7]. In either case, sleepiness results from both circadian misalignment and truncated sleep duration. In jet travel, it has been demonstrated that the endogenous circadian rhythm resets approximately 92 min later each day after a flight westward and approximately 57 min earlier each day after a flight eastward. Therefore it is more difficult to align the intrinsic rhythm with the external clock in eastward travel [9]. Alignment may occur in the opposite direction (referred to as *antidromic reentrainment*) when traveling across more than eight time zones [10]. In addition to the direction of travel

and sleep loss, other factors that may influence the severity of jet lag include the number of time zones crossed, exposure to and the magnitude of local circadian time cues (eg, alteration of light during various times of the year), and individual variance [11]. Thirty million US citizens traveled overseas in 2009, but the exact incidence of jet lag is unknown [12]. Although jet lag is usually benign and transient, it may become recurrent and problematic in those who travel frequently and may result in occupational hazard.

Therapeutic strategies

To understand the therapeutic strategies used in treating shift work disorder and jet lag, one must appreciate how circadian and homeostatic processes interact to regulate sleep and wakefulness. The master clock regulating the endogenous circadian rhythm is located in the suprachiasmatic nucleus (SCN) located in the anterior hypothalamus [5]. The cycle of sleep and wake is the most prominent circadian rhythm, with the highest propensity for sleep occurring near the nadir of core body temperature (occurring approximately 2 to 3 h before the usual wake time) [2].

This circadian process interacts closely with the homeostatic drive for sleep. SCN neurons are active during the subjective day and are stimulated by light. As the homeostatic drive for sleep accumulates with wakefulness, SCN activity increases to maintain alertness and then decreases in the evening, prior to sleep time [5], facilitating sleep. Interestingly, pineal melatonin begins to rise about 2 h before sleep onset [5]. As the homeostatic drive dissipates during sleep, SCN activity remains low. It has been postulated that melatonin helps to maintain sleep by its ability to inhibit the firing rate of the SCN neurons [5].

Light is the strongest cue synchronizing the circadian clock to the external environment [5]. After light is received by melanopsin-containing retinal ganglion cells, photic information is transmitted via the retinohypothalamic tract to the suprachiasmatic nucleus [2]. Light in the evening (before the core body temperature minimum is reached) delays the circadian rhythm, and light given in the morning (after the core body temperature minimum is reached) advances the circadian rhythm. The phase-response curve to light demonstrates that the magnitude of phase shift is greatest when light would usually be absent (during the night).

Melatonin is a hormone regulated by the SCN and secreted by the pineal gland. Melatonin levels begin to rise 1 to 3 h before the habitual sleep time and peak just prior to the core body temperature nadir [5]. In contrast to light, melatonin given in the evening shifts the circadian rhythm to an earlier time, and melatonin given in the morning shifts it to a later time. The phase-response curve to melatonin shows the largest magnitude of change occurring at the time when endogenous secretion is the lowest (during the day).

Treatment

- The treatment of shift work disorder and jet lag is multifaceted and includes strategies to achieve and maintain some degree of circadian alignment (Fig. 1), improve sleep (using hypnotics, melatonin, and behavioral approaches), and facilitate alertness (using light, wake-promoting agents and sleep scheduling) (Table 1). In addition, good general sleep hygiene is an integral part of managing both disorders. Measures include: regular sleep and wake times, routine exercise (but not within three hours of bedtime), abstaining from caffeine, nicotine, heavy meals, alcohol, and stressful or stimulating activities near bedtime, and creating an environment conducive for sleep [5].

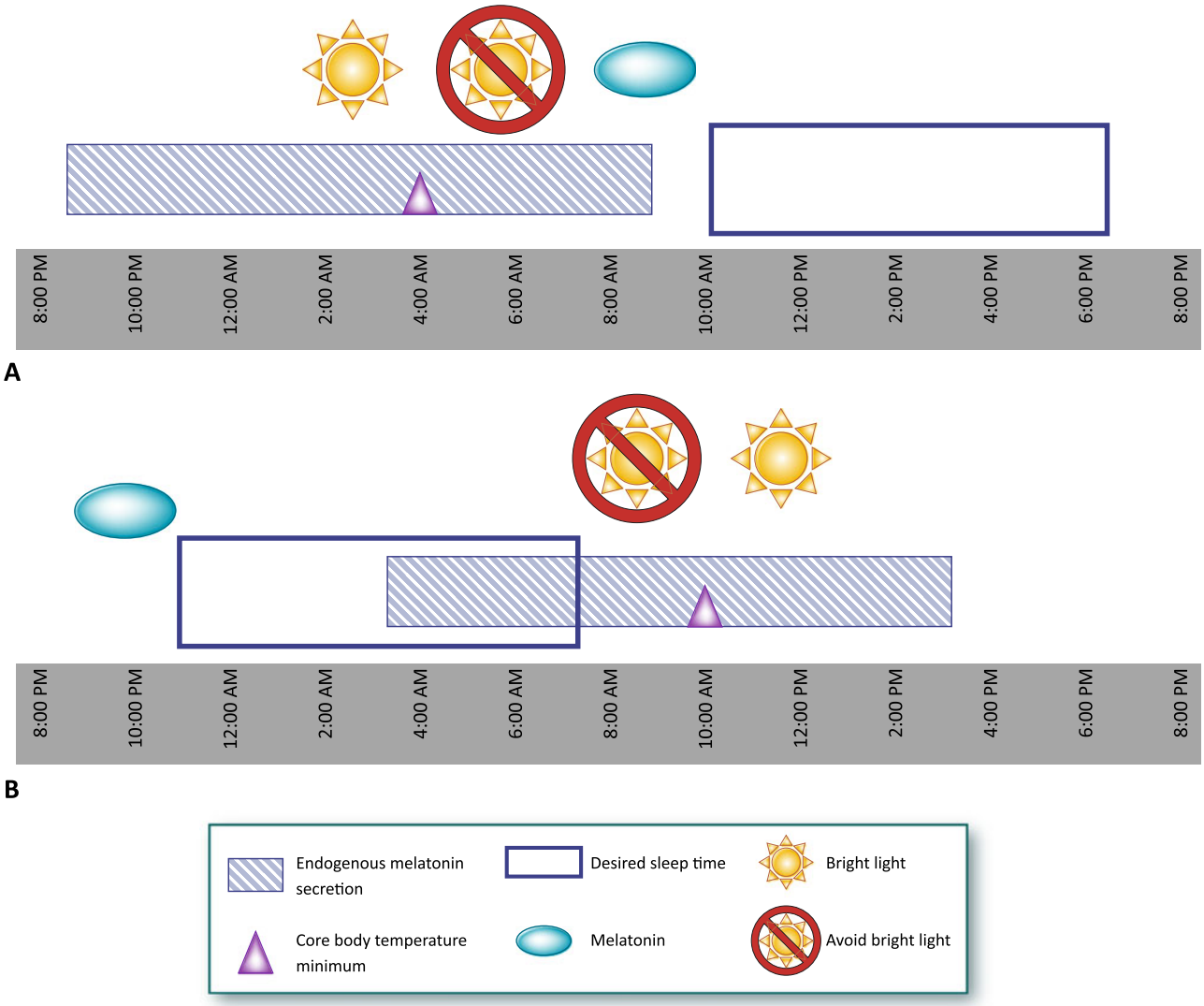

Figure 1. In an individual with normal circadian phase, dim-light melatonin onset occurs 7 h prior to core body temperature minimum, which is about 2 to 3 h before the usual wake time. The timing of the peak of melatonin secretion and core body temperature minimum are associated with a high circadian propensity for sleep and occur within the sleep period during normal conditions. A, In a night-work/day-sleep cycle, circadian sleep-promoting factors occur before the sleep period, so the goal is a phase delay to align the endogenous clock with the external environment with appropriately timed light, avoidance of light, and melatonin. B, With jet travel over six time zones east, the circadian propensity for sleep (as set by the origin of travel) falls after the desired sleep period at the local time in the destination. A phase advance with appropriately timed light and/or melatonin can accelerate circadian alignment. (*Adapted from* Kwon and Zee [5]).

Treating shift work disorder

Diet and lifestyle

Scheduled sleep times

By dissipating the homeostatic drive for sleep, napping is an effective strategy to counteract sleepiness in shift workers. Napping prior to night

Table 1. Treatment of shift work disorder

Treatment modality	Strength of recommendation
Planned napping	Standard[a]
Timed light exposure	Guideline[b]
Administration of melatonin prior to day sleep	Guideline[b]
Hypnotic medication to promote day sleep	Guideline[b]
Modafinil to enhance alertness	Guideline[b]
Caffeine to enhance alertness	Option[c]

[a]Standard—Generally accepted patient care strategy reflecting a high degree of clinical certainty.
[b]Guideline—Patient care strategy reflecting a moderate degree of certainty.
[c]Option—Uncertain clinical use.
(*Adapted from* Morgenthaler et al. [11].)

shift work has been associated with decreased accidents and improved alertness and performance. Beneficial effects of napping before night work were further augmented with caffeine administration [13, Class III; 14, Class I].

Naps of 20 to 50 min duration during shift work have produced improvements in reaction time and have restored performance to that seen at the beginning of the shift. In addition, napping early in the night shift improves objective measures of alertness [15, 16; Class II]. If the nap duration is greater than 30 min, some degree of sleep inertia may occur [15, Class II].

No disruption of the main sleep period occurred secondary to the nap [16, Class II; 17, Class IV]. Planned napping is considered a standard of care in the treatment of shift work disorder by the American Academy of Sleep Medicine (AASM) [11].

Melatonin

The AASM recommends melatonin prior to day sleep as a treatment guideline for shift work disorder [11]. Exogenous melatonin has effects of both resetting the circadian clock and acting as a direct hypnotic [10].

In a randomized, controlled trial of 32 individuals undergoing simulated night work with attempted sleep occurring in the afternoon and evening, melatonin at doses of 3 mg or 0.5 mg or a placebo was given prior to the nonconventional sleep period. Both doses of melatonin resulted in a significant phase advancement (3 h for 0.5 mg and 3.9 h for 3 mg), compared with placebo [18, Class I]. In addition to shift work simulation, the clock resetting effects of melatonin have also been demonstrated in some night workers during field studies [19, Class I].

The addition of melatonin did not augment circadian adaptation in the setting of a treatment strategy using bright light therapy during the night shift and light avoidance in the morning [20, Class II].

Melatonin (1.8–6 mg), given prior to day sleep, has been shown to improve total sleep duration in both simulated night shifts and studies of night workers [21, Class I; 22, Class III; 23, Class II].

No improvements in nighttime alertness have been seen with the use of melatonin [21, Class I; 24, 25, Class II].

No field studies or simulated studies of early morning shift work using melatonin are currently available. However due to the known efficacy of exogenous evening melatonin in advancing circadian rhythms, melatonin may be a rational treatment option for shift work requiring an early rise time. Further studies are needed.

Caffeine

The AASM suggests caffeine as a treatment option to enhance alertness during night work [11].

It is well known that caffeine can be an effective countermeasure for sleepiness during experimentally induced sleep deprivation, making it a feasible option for treatment in shift work disorder and jet lag [8••].

In a double-blind, randomized, placebo-controlled trial of 15 individuals performing simulated night work, coffee (2 mg/kg dose of caffeine) was given immediately prior to and during the first portion of the night shift. There was significant improvement in sleepiness as measured by the multiple sleep latency test, and participants rated themselves as 25% more alert. There was no residual effect on daytime sleep as measured by polysomnography [26, Class I].

A recent meta-analysis found that caffeine (compared with placebo) improved shift workers' performance in multiple domains of neuropsychiatric testing, including memory and attention [27].

Pharmacologic treatment

Benzodiazepines and benzodiazepine receptor agonists

Hypnotic medications have been evaluated for shift work disorder, specifically for the treatment of insomnia occurring as a result of attempting sleep during the period of high circadian alerting signal.

Triazolam (0.25–0.5 mg) and temazepam (20 mg) have been shown to be effective in increasing daytime sleep duration with both subjective and objective measures. No improvements in nighttime alertness (by self report or by mean sleep latency testing) have been demonstrated with either medication, however [28, 29, Class I; 30, Class III; 31, Class II].

Two field studies of shift workers using zopiclone also showed subjective improvements in sleep quality and duration, but there was no evidence of improvement in work performance [32, Class I; 33, Class II].

In a study of seven individuals undergoing simulated rotating shifts, those receiving zolpidem had improved subjective sleep quality, but their mood was worsened during the following work period, compared with placebo [34].

In the AASM practice parameters, the use of hypnotic medication is a treatment guideline to facilitate day sleep in night workers. These agents should be administered with great caution when used for insomnia during the nonconventional sleep period, however, because of the potential for unfavorable effects on nighttime performance and alertness [11]. Further studies are needed to determine the efficacy

of benzodiazepines and benzodiazepine receptor agonists in shift work disorder.

Standard dosage Benzodiazepine and benzodiazepine receptor agonist medications are not approved by the US Food and Drug Administration (FDA) for the specific purposes of treating shift work disorder or jet lag. However, for short-term insomnia, temazepam (7.5–30 mg) or zolpidem (5–10 mg) may be used at bedtime [35, 36]. Zopiclone is not available in the United States.

Contraindications Temazepam and zolpidem should be used with care in elderly and debilitated patients, and alcohol should not be used with either. With temazepam, slow tapering of the medication should be performed prior to discontinuation because of a risk of seizure with abrupt cessation. Zolpidem is a pregnancy category C medication. Pregnancy is an absolute contraindication to temazepam use because of its class X designation [35, 36].

Main drug interactions Central nervous system depressants may have an additive effect with temazepam and zolpidem. Oral contraceptive pills may increase the clearance of temazepam, and probenecid may decrease its clearance [35, 36].

Main side effects The most frequently reported adverse effects of zolpidem are daytime drowsiness, headache, and dizziness. Amnesia may occur with benzodiazepine and benzodiazepine receptor agonist medications, and non–rapid eye movement (NREM) parasomnias such as sleep walking or sleep eating also may occur. The most common adverse effects of temazepam are headache, drowsiness, ataxia, dizziness, confusion, depression, syncope, fatigue, vertigo, and tremor. Patients should be monitored for physiologic dependence on temazepam [35, 36].

Cost/Cost-effectiveness Both zolpidem and temazepam are less than $20 for a 30-day supply, making them cost-effective treatment options.

Wake-promoting medications

Because night shift work occurs during a time of high propensity for sleep, wake-promoting medications have been investigated to improve alertness in shift workers.

In one study, methamphetamine improved mood and performance during the night shift in simulated laboratory workers [37, Class II]. However, because of the minimal evidence supporting its use and its potential for abuse, this medication is not indicated in the treatment of shift work disorder [11].

In a randomized double-blind controlled trial, modafinil (200 mg) was given 30 to 60 min before the start of night shift work, resulting in objective improvement in sleepiness and improved performance on psychomotor vigilance testing. In addition, there were 25% fewer accidents and near-accidents in the modafinil group than in the placebo group ($P<0.001$). Despite these functional improvements and the attenuation of sleepiness, a pathologic level of sleepiness similar to that of narcolepsy (mean sleep latency, 3.8 min) persisted in night shift workers [38, Class I].

Armodafinil is the R isomer of modafinil and has a longer half life (15 h) than the S isomer of modafinil (3–4 h). In a 12-week randomized controlled trial of 254 night shift and rotating shift workers with shift work disorder, 150 mg of armodafinil was given 30 to 60 min prior to beginning the night shift. Armodafinil resulted in a significant increase in

mean sleep latency compared with placebo (3 min vs 0.4 min respectively). By self-report, armodafinil reduced sleepiness during work and on the morning commute. Significant improvement in performance on standardized memory and attention testing was also demonstrated. No worsening in daytime sleep parameters occurred with armodafinil [39•, Class I].

Modafinil and armodafinil are effective in promoting alertness during night shift work and are FDA-approved for the treatment of shift work disorder.

Standard dosage Modafinil (200 mg) or armodafinil (150 mg) taken approximately 1 h prior to shift work.

Contraindications Patients with cardiac signs or symptoms occurring in the setting of stimulant medication should not take modafinil or armodafinil. Caution should be exercised in prescribing these medications for patients with a known history of psychosis, unstable angina, or recent myocardial infarction, and those with seizures. Both drugs are FDA pregnancy category C [40, 41].

Main drug interactions Modafinil and armodafinil may decrease the effectiveness of oral contraceptive pills and other drugs metabolized by the CYP3A4 isoenzyme, and drugs inducing the CYP3A4 enzyme may increase the metabolism of modafinil and armodafinil [40, 41].

Main side effects Rare but life-threatening rashes have occurred with modafinil therapy [40]. Headache, nausea/vomiting, anxiety, nervousness, and insomnia were the most common adverse reactions occurring in clinical trials of modafinil [40]. Headache, nausea/vomiting, dizziness, and insomnia were the most common adverse reactions occurring in clinical trials of armodafinil [41]. Some individuals taking armodafinil had a small elevation in blood pressure [41].

Cost The retail price for a 30-day supply is $475.95 for modafinil (Provigil; Cephalon, Frazer, PA) and $304.97 for armodafinil (Nuvigil; Cephalon, Frazer, PA).

Other treatments

Timed bright light exposure

Timed light exposure can be employed for its circadian phase shifting effects as well as its beneficial effects on alertness and cognitive performance [42]. The AASM suggests the use of timed light during the work period and restriction of morning light in night shift workers as a treatment guideline [11].

In field studies of shift workers, light regimens of 2350 to 12,000 lux for durations of 20 minutes (with multiple exposures) to 6 h have shown improvements in psychomotor performance, subjective alertness, and self-rated mood [43, 44, 45, Class III].

Bright light exposure and the avoidance of light have been used to promote circadian shifts to move the core body temperature nadir from the work period to the sleep period. Studies using this treatment strategy have been performed in both night work simulation and in field testing of actual night workers [5]. Bright light of 6000 to 12,000 lux during at least half of a 12-hour night shift resulted in a significant phase shift in 50% of shift workers receiving the treatment, compared with controls

receiving ambient light [44, Class III]. The largest phase shifts and improvements in subjective sleep quality have occurred in groups using both interventions: bright light during the night shift combined with light avoidance (using dark sunglasses or goggles) the following morning [23, 46; Class II].

Despite the benefits in performance and alertness produced by aligning the circadian rhythm to night work, many patients may be reluctant to do so, as they want to realign their phase to a conventional diurnal waking schedule on days off. One group has proposed the idea of partial alignment using a goal "compromise position" with the core body temperature nadir near 10:00, which puts the highest circadian propensity for sleep early but within the sleep period on work days and late but within the sleep period appropriate for days off. This compromise position was achieved with bright light, light avoidance, and scheduled sleep times (08:30 to 15:30 on work days and 03:00 to 12:00 on days off). Sleep after the last night shift was truncated to 08:30 to 13:30 in anticipation of an earlier bedtime on the days off. The subjects aligning to the "compromise position" had mood, fatigue, and performance ratings that were markedly superior to controls and were similar to those of subjects completely entrained to a night-wake, day-sleep schedule. This partial entrainment strategy may be an effective strategy for permanent night workers to improve function on both work days and days off [47•, Class II].

Standard procedure Although no standard protocol for bright light therapy exists, studies have been performed with both intermittent and sustained exposures of 2350 to 12,000 lux. Ultraviolet wavelength light should be filtered [48]. Light therapy treatment is not regulated by the FDA.

Contraindications Patients with retinopathies should not receive treatment with bright light therapy. Great care should be taken in those using medications causing photosensitization and patients with bipolar disorder [48].

Complications Hypomania, irritability, nausea, headache, blurred vision, eye strain, photophobia, and sleep disturbances are the most frequently reported adverse reactions. Side effects are uncommon, may depend on dose and timing, and may resolve over time [48].

Cost/Cost-effectiveness Light boxes range in price from about $200 to $500. As a one-time investment, this may be a cost-effective option.

Treating jet lag

Diet and lifestyle

Scheduled sleep times

In jet lag, sleep scheduling is used as an adjunct to light in shifting the circadian rhythm.

For travel of greater than 48 h, travelers could attempt to shift their circadian rhythm prior to departure. In a study to determine how much bedtimes could be shifted (while using bright light therapy) in preparation for eastward travel, subjects advancing bedtimes by 2 h per day experienced greater sleep-onset insomnia than those advancing by 1 h per day. Jet lag scores were similar between both groups on most days of

treatment. Therefore, advancing bedtime by 1 h per day in combination with light therapy may be a useful intervention in the anticipation of eastward travel [49, Class II]. This sleep schedule advance prior to travel east is recommended as a treatment option by the AASM [11].

However, for travel less than 48 h, those maintaining the sleep/wake times of the location of origin reported decreased sleepiness and better global jet lag ratings than those adopting the sleep/wake times of the destination location during a study of travel over nine time zones [50, Class II]. The AASM suggests keeping home sleep and wake times during travel of 2 days or less as a treatment option [11].

Exposure to and avoidance of natural light

Bright light therapy has demonstrated significant augmentation of phase shifts in simulated studies of eastward travel. (See the discussion of timed light exposure below.) However, although this phase shift may attenuate circadian misalignment, bright light therapy may be inconvenient during travel, making the exposure to and avoidance of natural light (using dark sunglasses) a more feasible treatment for jet lag.

During westward travel, the goal is to delay the circadian rhythm, so light exposure should be sought during what would be evening in the location of departure and avoided during what would be morning in the location of departure. For eastward travel, to initiate a phase advance, light should be avoided during what would be evening in the location of departure, and light exposure should occur during what would be morning [51].

This strategy is best illustrated by example. If a traveler lives in Chicago and usually sleeps from 11 PM to 7 AM, his core body temperature minimum (assuming normal circadian phase) would likely be close to 4 AM (11 PM Hawaii time). If he departs from Chicago at 0900 and lands in Hawaii at 1600 (local time), he needs to get plenty of afternoon and evening light and avoid bright light in the morning. Conversely, if he travels from Chicago to Paris (where his core body temperature minimum would be at 11 AM), departing at 1800 and arriving at 1100 (local time), he should seek plenty of afternoon light and avoid morning light prior to 11 AM. This example also demonstrates that some degree of phase shifting prior to eastward travel may be beneficial to move the core body temperature minimum to the dark period, preventing light exposure during the wrong portion of the phase-response curve [52].

Melatonin

In multiple studies for jet lag, melatonin has shown benefits likely due to both its phase shifting and sedating effects.

Of nine double-blind, placebo-controlled field studies evaluating the effects of melatonin on subjective measures of jet lag, seven studies showed more favorable ratings of symptoms with melatonin than with placebo. These studies used 0.5 mg to 8 mg (most commonly 5 mg) of melatonin for travel of up to 12 time zones [8••].

Objectively, melatonin has demonstrated increased total sleep time and decreased waking after sleep onset (as measured by actigraphy), compared with placebo [53, Class I].

Melatonin has also shown acceleration of phase shift during travel, as measured by cortisol and melatonin rhythms [54, 55, 56].

Appropriately timed melatonin use, to improve both sleep and waking symptoms, is considered a standard treatment for jet lag by the AASM [8••].

Caffeine

Caffeine has been evaluated in jet lag in two studies, both with 27 subjects traveling eastward over seven time zones. Slow-release caffeine (300 mg) given at 0800 the first 5 days after arrival improved objective measures of daytime sleepiness and accelerated circadian entrainment, as measured by cortisol rhythms. Caffeine did result in greater subjective and objective sleep disruption than placebo [54, 57; Class II].

The AASM suggests caffeine as a treatment option for daytime sleepiness related to jet lag [11].

Pharmacologic treatment

Benzodiazepine and benzodiazepine receptor agonists

The benzodiazepines temazepam, midazolam, and triazolam have been evaluated for the treatment of jet lag in four studies. In eastward travel, temazepam and midazolam showed improvement in subjective sleep quality and objective sleep measures by actigraphy, but no benefits were noted in westward travel [8••].

Zolpidem (10 mg) has demonstrated improved sleep quality and duration, as well as improvement in jet lag symptoms, after eastward travel, but adverse effects (including nausea, vomiting, amnesia, and somnambulism) were greater with zolpidem than with melatonin or placebo [58, 59; Class I].

Zopiclone has also shown increased sleep duration (as measured by actigraphy) in one study of eastward flight and one study of westward flight, compared with placebo, but no improvement in sleep measures was shown in comparison with melatonin, and there is no evidence that this hypnotic improves symptoms of jet lag [53, Class I; 60, Class II].

The AASM does suggest benzodiazepine receptor agonist hypnotic therapy as a treatment option for short-term insomnia resulting from jet lag. However, more research is needed regarding the effect of these agents on waking jet lag symptoms, and patients must be educated about potential side effects [11].

Other treatments

Timed light exposure

In jet lag, light therapy has been used with the goal of shifting circadian rhythms prior to departure. For example, in a study using either intermittent or continuous bright light therapy in the first 3.5 h after awakening (combined with advancing sleep schedules), subjects in the bright light group reset their clock 1.5 to 2 h earlier after 3 days of treatment, versus 0.6 h in the

control group. In addition, those receiving continuous light did not have a worsening in their jet lag score with advancing bedtimes, as did those receiving intermittent or no bright light [61, Class II].

In a field study of westward travel (Zurich to New York), light was used to delay the circadian rhythm after arrival. Although a greater phase delay occurred with bright light therapy, there was no difference in jet lag scale, psychomotor performance, or mood [62, Class II].

Morning bright light therapy (in combination with advancement of the sleep schedule) before travel east is recommended as a treatment option by the AASM.

Emerging therapies for shift work disorder and jet lag

Transdermal melatonin

The homeostatic drive for sleep is dissipated by sleep occurring during the initial portion of the sleep period. During the night, this is counteracted by the circadian propensity for sleep, partly due to the inhibitory effects of melatonin on the SCN [5]. Because night workers are sleeping during the "wrong" circadian time, they lack this mechanism for sleep maintenance.

When 2.1 mg of melatonin (compared with placebo) was given transdermally 1 h before an 8-hour daytime sleep opportunity, waking after sleep onset and in the latter third of the sleep period decreased, sleep efficiency increased, and total sleep time increased. Although melatonin levels remained elevated after the sleep period, subjective alertness and visual attention were not affected, as measured by the Karolinska Sleepiness Scale and psychomotor vigilance testing [63].

A sustained-release method of delivering melatonin may be an effective option for sleep-maintenance insomnia in those with a nonconventional day sleep schedule, but more studies are needed.

Melatonin receptor agonists

Melatonin has produced marked improvement in jet lag symptoms and mixed effects in the treatment of shift work disorder. Because melatonin varies in potency and quality and is not regulated by the FDA, a melatonin receptor agonist may be a promising treatment for shift work disorder and jet lag.

Ramelteon is an MT_1 and MT_2 receptor agonist. In a study to determine the ability of ramelteon to realign the circadian rhythm after an imposed 5-hour advance of sleep-wake times in 75 healthy adults, ramelteon was given 30 min prior to the new bedtime. A significant circadian shift to an earlier time occurred in patients receiving 1 mg, 2 mg, or 4 mg of ramelteon, compared with placebo. Headache and nausea were the most commonly experienced adverse reactions and were mild in severity [64, Class I].

In a recent randomized, double-blind, placebo-controlled trial, 109 individuals with a history of jet lag were given 1 mg, 4 mg, or 8 mg of ramelteon or placebo at their usual bedtime after arrival following eastward travel of five time zones. On all nights following travel, with a 1-mg dose of ramelteon, there was a significant reduction of latency to

persistent sleep (-10.6 min, $P=0.03$) as compared with placebo. When further examining two subsets of the study (those exposed to natural light and those kept in dim light conditions), the group exposed to natural bright light and taking a placebo experienced sleep-promoting effects similar to the effects on those in dim light who received 1 mg of ramelteon. Therefore, ramelteon could be a treatment option during travel when bright light is less accessible (eg, during the winter). There were no significant differences between the ramelteon group the placebo group in sleepiness scales during waking hours. At the 4-mg dose, significant improvements in subjective daytime function, alertness, concentration, sleep quality, and ease of awakening were seen. Adverse effects were similar across all groups [65•, Class I].

Tasimelteon is another MT_1 and MT_2 receptor agonist. In a phase 3, double-blind, randomized placebo-controlled trial, 411 individuals underwent a 5-hour advance of sleep-wake times and received tasimelteon at the new bedtime. Compared with placebo, all doses of tasimelteon were followed by decreased latency to persistent sleep onset, decreased waking after sleep onset, increased total sleep time, and increased sleep efficiency. Results of neurocognitive testing the day after treatment were no different with tasimelteon or placebo [66, Class I].

Agomelatine (also an MT_1 and MT_2 receptor agonist, as well as a serotonin agonist) has been shown in a double-blind, placebo-controlled trial to significantly phase-advance body temperature profiles [67].

The clock-advancing properties of melatonin agonists may be effective in treating shift work disorder resulting from early morning shifts as well as jet lag resulting from eastward travel.

Wake-promoting agents

Although approved for shift work disorder, armodafinil does not currently have an indication in jet lag.

In a recent double-blind, randomized, placebo-controlled study to determine the efficacy of armodafinil in jet lag, 427 individuals traveled eastward over six time zones and were given armodafinil (50 mg or 150 mg) or placebo daily at 7 AM local time after arrival. Those receiving 150 mg of armodafinil had significant improvements in objective measures of sleepiness (mean sleep latency on the Multiple Sleep Latency Test of 11.7 min vs 4.8 min with placebo, $P<0.001$) and less severe symptoms of jet lag [68•, Class I].

Armodafinil may be an effective agent for combating daytime sleepiness associated with jet lag.

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