CHEST Postgraduate Education Corner

CONTEMPORARY REVIEWS IN SLEEP MEDICINE

Air Travel

Effects of Sleep Deprivation and Jet Lag

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Air travel is a common mode of transportation in today's society, particularly for individuals traveling long distances. Sleep disturbances associated with air travel frequently result in cognitive and physiologic impairments that may be detrimental to the traveler's experience and intent. A primary consequence of air travel is the development of acute sleep deprivation, which may result in reduced attention/vigilance, alteration in mood states, diminished memory processing, and alteration in executive function. Along with and contributing to acute sleep deprivation, circadian rhythm misalignment resulting in jet lag disorder (JLD) is frequently encountered by air travelers traversing multiple time zones. JLD is characterized by insomnia or excessive daytime sleepiness associated with physical or mental impairment associated with travel. This review focuses on the neurocognitive manifestations of acute sleep deprivation and the pathophysiology and treatment of JLD to provide the practicing clinician a greater understanding of the sleep abnormalities manifest in air travelers. Treatment recommendations for the traveler, including the use of light/melatonin therapy, sleep scheduling, and pharmacologic aids for both sleep and alertness, are provided. ***CHEST 2013; 144(4):1394–1401***

Abbreviations: JLD = jet lag disorder; PVT = psychomotor vigilance task; SCN = suprachiasmatic nucleus

Travel is a part of everyday life for most individuals. Long-distance air travel is quite common and increasing in frequency. In 2010, 787 million passengers traveled by plane in the United States (domestic and international). International travel on both US and foreign carriers increased by 3.2% from 2009 to 2010.[1] During long-distance travel, sleep is frequently disrupted, and the ensuing sleep deprivation plays a central role in the clinical manifestations of both travel fatigue and jet lag disorder (JLD). In this article, we hope to increase the reader's understanding of the neurocognitive manifestations of acute sleep deprivation and the basic mechanisms of circadian regulation to elucidate the manifestations and therapeutic options in the management of JLD.

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Sleep Deprivation

Although the optimal duration of daily sleep for an individual is unknown, most young adults obtain 7.5 to 8.5 h per night.[2] Despite the characterization of a subgroup of individuals who are considered "naturally short sleepers" requiring only 3 to 6 h of sleep per night,[3] several large observational studies have demonstrated the deleterious effects of sleep duration of <7 h per night.[4,5] For purposes of this review, sleep duration of <6 to 7 h per sleep period is considered sleep deprivation.

Sleep deprivation is common and may be increasing in prevalence.[6] A report of the National Health Interview Survey in 2010 estimated that among all employed civilian adults in the United States, 30% (40.6 million workers) reported an average sleep duration of ≤ 6 h per night.[7] The high prevalence of sleep deprivation is quite concerning, particularly in light of its effects on daytime alertness. Sleep loss is a well-known risk factor for accidents in the transportation and other industries due to decreased vigilance and falling asleep while working.[8] Sleep deprivation is commonly separated into three subtypes within the medical literature: acute sleep deprivation, chronic

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sleep deprivation, and sleep fragmentation. Although there are differences in the cognitive manifestations of the different types of sleep loss, there is also a great deal of overlap. As acute sleep deprivation is present in long-distance air travelers[9] and plays an important role in development of neurocognitive abnormalities during wakefulness, this review focuses on this aspect of sleep loss.

Effects on Attention and Vigilance

Attention and vigilance are crucial for optimal daytime function. A well-validated measure of vigilance, the psychomotor vigilance task (PVT),[10] is frequently used to measure reaction time to a stimulus as well as errors of omission and commission of the stimulus. In a study of 28 subjects assigned to 88 h of total sleep deprivation vs 88 h along with two 2-h naps, the total sleep deprivation group demonstrated worsened reaction time as determined by the PVT compared with the nap group.[11] Additionally, the total sleep deprivation group had increased variability in PVT measures. In a meta-analysis that included 147 datasets with a sample size of 1,533 subjects,[12] the largest effect of 24 to 48 h of sleep deprivation was seen in the tests of vigilance ("simple attention"), resulting in a moderate to large effect. Other cognitive domains showed progressively less robust findings: working memory, complex attention, short-term memory, processing speed, and reasoning (decreasing order of effect size).

Loss of attention and vigilance likely plays a role in motor vehicle accidents related to drowsy driving. Motor vehicle crashes are frequently attributed to driver sleepiness, accounting for 1% to 3% of all motor vehicle crashes in the United States.[13] Although driver sleepiness is not solely caused by sleep deprivation (circadian timing of driving also plays a strong role), acute sleep deprivation is a frequent finding. Out of 2,196 stops at a freeway toll plaza, 50% of subjects reported decreased total sleep in the 24 h prior to being interviewed when compared with their normal sleep time, and 4.4% slept < 4 h in the same time frame.[14] Among drivers who stopped at a highway rest stop, mean sleep onset latency was significantly decreased compared with control subjects on a "two-nap sleep test," whereas the sleep onset latency was < 5 min among subjects during nap 1 in 25% (26 of 104) and during nap 2 in 13% (14 of 104),[15] clearly demonstrating increased objective sleepiness, which may impair driving performance.

Effects on Mood and Emotional State

Important for both recreational and business travelers, mood and emotional state are significantly affected by acute sleep deprivation. Total sleep deprivation for a single night resulted in increased negative mood and negative perception of neutral images, whereas the subject's perception of a pleasant or unpleasant image was unchanged compared with control subjects.[16] The perception of neutral images with increased negativity was independent of the subject's mood. In healthy volunteers sleep deprived for 56 continuous hours, the Personality Assessment Inventory scale demonstrated increased levels of somatic complaints, anxiety, depression, and paranoia to subclinical levels.[17] Besides the effects of acute sleep deprivation, travel over a large number of time zones appears to increase the risk of exacerbation of preexisting psychiatric disease presumably due to circadian mismatch (discussed later).[18] Whereas alterations in emotional state and increased psychiatric symptoms may be distressing, the importance of emotional intelligence and its relation to critical thinking, particularly for the business traveler, must not be understated. As outlined by Killgore et al,[19] emotional intelligence, or the ability to act and think constructively by using an individual's own emotional and empathic abilities, is crucial for adaptive problem solving and coping skills in highly stressful situations. In their study on self-perceived emotional intelligence and constructive thinking patterns, sleep deprivation of approximately 55 to 58 h resulted in significantly lower scores among several scales, including self-regard, empathy, interpersonal relationships, impulse control, and behavioral coping. Particularly for the business traveler in a highly stressful situation, the ability to think and act in a constructive manner according to emotional cues is essential.

Effects on Learning and Memory

Sleep is essential to learning and memory processing. Accumulating evidence suggests that sleep deprivation can affect learning (memory encoding) and memory consolidation. Functional MRI has been used to investigate the different sites and degree of brain activity associated with learning. Yoo et al[20] demonstrated that 35 h of total sleep deprivation was associated with both decreased visual recall of newly formed memories as well as decreased activity in the hippocampus, thus demonstrating a diminution of memory encoding along with its neural correlate. The emotional nature of a learned task had an important effect on a subject's ability to recall a learned stimulus in the setting of sleep deprivation. Subjects who underwent sleep deprivation for 36 h, compared with a control group with normal sleep, were presented with sets of emotion-laden words that were positive, negative, or neutral. After two nights of normal sleep, the subjects demonstrated a 40% overall reduction in memory

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retention as compared with control subjects; however, when separated by emotional content, the greatest decline in recall occurred for the emotionally positive word sets and not for the neutral and negative word sets.[21] These findings suggest that memory encoding is decreased in sleep-deprived individuals, although this is modulated by the emotional status of the memory. This may be a mechanism by which even sleep-deprived individuals remember negative states to protect themselves from future negative events.

Executive function is exceedingly important for the traveler, particularly the business traveler who must rely on higher-order cognitive function to solve and respond to complex problems. According to *Kaplan & Sadock's Comprehensive Textbook of Psychiatry*, executive functions include "volition (i.e., formulation of a goal, motivation to achieve the goal, and awareness of one's own ability to achieve the goal), planning, purposive action (response selection and initiation, maintenance, switching, and stopping), and execution, which involves self-monitoring and self-correction as well as control of the spatiotemporal aspects of the response."[22] In an excellent review of the cognitive effects of sleep deprivation, Killgore[23] suggests that consistent results in experimental data on executive tasks are lacking, likely due to differentially affected regions of the brain following sleep deprivation and the complexity of the cognitive processes studied. For example, deductive reasoning appears to not be affected by sleep deprivation, whereas innovative thinking is likely affected (ie, fewer original ideas and increased response redundancy). Risk taking and decision-making are likely affected by sleep deprivation, which may have dire consequences in the business traveler who is sleep deprived. Subjects who were sleep deprived for 49.5 h demonstrated significantly higher risk taking in the Iowa Gambling Task when compared with baseline levels.[24] Although the exact mechanism is unknown, subjects in this study demonstrated findings similar to those with lesions in the ventromedial prefrontal cortex, which may be a target in sleep-deprived individuals. Additionally, sleep deprivation may increase risk-taking behavior by precipitating hypomania or mania in susceptible individuals.[25] Although there is still much to be worked out regarding sleep deprivation and executive function, it is clear that sleep-deprived individuals may act differently in the sleep-deprived state, which may ultimately be disadvantageous.

Other Physiologic Effects

Besides neurocognitive abnormalities, acute sleep deprivation is also associated with important and varied physiologic changes. There is evidence that hypoxic and hypercapnic ventilatory responses are blunted with acute sleep deprivation.[26] Sleep deprivation can elicit seizure activity in patients with epilepsy.[27] Cardiovascularly, BP increases with sleep deprivation, whereas autonomic parameters are affected variably.[28] Sleep deprivation has also been associated with alterations in metabolism, including glucose metabolism and changes in leptin and ghrelin levels.[29] Further discussion of physiologic changes associated with acute sleep deprivation is beyond the scope of this article.

Circadian Rhythm and JLD

JLD is a circadian rhythm sleep disorder that is associated with air travel traversing several time zones. In contrast, travel fatigue is characterized by general fatigue, disorientation, and headache, and travel weariness due to disruption of normal sleep patterns, dehydration, and the stressors of travel.[30] Travel fatigue may be seen with any long journey (not exclusive to air travel) and usually resolves after a good-quality sleep period. Travel conditions within the airplane may contribute to some of the distress experienced by travelers (both travel fatigue and jet lag symptoms).[31] For example, expansion of gas within the GI system (due to lowered cabin pressure) may result in discomfort/bloating, lower inspired oxygen may affect patients with respiratory conditions, motion sickness may present itself, and low relative humidity may result in dehydration, although the degree of dehydration is likely minimal.[32]

The diagnostic criteria for JLD are as follows: (1) there is a complaint of insomnia or excessive daytime sleepiness associated with transmeridian jet travel across at least two time zones; (2) there is associated impairment of daytime function, general malaise, or somatic symptoms such as gastrointestinal disturbance within 1 to 2 days after travel; and (3) the sleep disturbance is not better explained by another current sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.[33] JLD is caused by the circadian misalignment between home clock time and destination clock time resulting in abnormal sleep patterns at the destination and the symptoms previously outlined. Thus, the individual experiencing JLD may feel a marked homeostatic drive to sleep and reduced circadian alerting stimulus during the middle of the day at their destination when wakefulness is most desired. Likewise, circadian alertness may be maximal in the middle of the night at their destination, resulting in poor quality or inability to sleep at the desired local time.

Circadian Rhythmicity

Sleep regulation is often described as a "two-process model"[34]: (1) the homeostatic process (process S) is

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responsible for the drive for sleep that accumulates throughout the day, is dependent on wake time and prior sleep duration, and is possibly related to the accumulation of adenosine in the basal forebrain[35] and (2) the circadian process (process C) is a rhythmic stimulus, independent of the homeostatic process, which drives the wake/sleep pattern over a 24-h period. Because of the finding that the human circadian rhythm is usually >24 h,[36] the rhythmic circadian process, which is mediated by the master circadian clock, the suprachiasmatic nucleus (SCN) located in the hypothalamus, is continually adjusted by zeitgebers ("time givers"), of which light exposure is the strongest modulator, whereas other nonphotic cues, including meals and other regular activities, show modest effect.[37] In contrast to the two-process model and based on studies of lesions in the SCN of squirrel monkeys, another model that builds on the two-process model is the "opponent process" of sleep/wake regulation proposed by Edgar et al,[38] in which circadian rhythmicity modulated in the SCN results in an alerting stimulus that "opposes" the homeostatic drive for sleep; thus, when the circadian alerting stimulus declines at bedtime, the unopposed homeostatic drive for sleep results in sleep initiation.

Although zeitgebers are important regulators of SCN output and continually adjust the circadian period, melatonin plays a similarly important role in circadian modulation. Melatonin is produced in the pineal gland, and its secretion is regulated via signals in the SCN; melatonin is secreted during dark and is inhibited during light.[39] Melatonin receptors are present in the SCN, thereby creating a feedback loop, and throughout the rest of the body, contributing to circadian signals in many tissue types throughout the body.[40]

The importance of the light/dark cycle and melatonin for regulation of circadian rhythmicity must not be understated; in fact, their interaction with the master circadian clock may be used as a treatment modality for various circadian rhythm sleep disorders, JLD being a prime example. Both light and melatonin have demonstrated phase response curves (mathematical and graphical representations of the expected response in circadian shift with application of a specific stimulus).[41,42] Indeed, light has been shown to induce a phase delay when administered in the evening and phase advance when exposed in the morning. The circadian effects of light exposure are exquisitely sensitive to the timing of exposure during the phase response curve. The crossover point of the curve occurs at the core body temperature minimum, and on either side of this point, the effect of light on phase shifting is maximal; thus, exposure and avoidance of light for therapeutic phase shifts must be appropriately timed. In contrast to light, melatonin given in the morning causes a phase delay but when given in the afternoon/evening results in a phase advance. These observations have led to numerous studies of therapy for circadian rhythm sleep disorders using timed light exposure and melatonin administration.

Jet Lag Disorder

As described in the *International Classification of Sleep Disorders* diagnostic criteria,[33] JLD results in diverse symptoms. Sleep disturbance is the most obvious abnormality in travelers, in which difficulty initiating and maintaining sleep and sleep fragmentation result in sleep deprivation. Cognitive abnormalities associated with sleep deprivation as described previously in the article as well as significant excessive daytime sleepiness are the end result of this poor sleep consolidation/duration. In general, because of endogenous circadian rhythmicity longer than a 24-h period, westward travel is tolerated better than eastward travel; a phase delay (staying up later than usual) is easier than the eastward phase advance. Estimates of the rate of resynchronization of clock time and circadian time range between 1 and 1.5 h per day.

JLD is managed by three modalities: light/melatonin administration, sleep scheduling, and pharmacologic treatment (Table 1). Administration of exogenous light and melatonin results in a shift of an individual's circadian rhythm according to the phase response curves. As stated earlier, evening light and morning melatonin results in phase delay (body clock shifts later, sleep propensity occurs at a later clock time), and morning light and evening melatonin results in phase advance (body clock shifts earlier, sleep propensity occurs at an earlier clock time) (Fig 1). Experimentally, timed light and melatonin administration have resulted in circadian shifts for all instances except morning melatonin administration for phase delay.[45] Although not thoroughly studied in a randomized, controlled fashion, sleep scheduling prior to and following travel likely plays an important role in circadian shifts, particularly as eye closure during a sleep period enables endogenous melatonin release and may hasten circadian realignment. Finally, several studies have looked at both hypnotic and stimulant therapy to improve JLD symptoms.

Melatonin and light administration have been the most extensively studied treatments for JLD. In a meta-analysis of 10 trials looking at melatonin taken at bedtime at a destination, Herxheimer and Petrie[46] concluded that melatonin is very effective in treating JLD, particularly in individuals traveling eastward (phase advance). Further trials addressing this issue since the publication of the meta-analysis confirm this finding both in the laboratory and in field studies.[47,48] Although melatonin does accelerate phase adjustment in JLD, the degree of effect is unknown; limitations of current studies include the subjective nature of

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Table 1—*Management of Jet Lag Disorder*

Flight Time	Strategy
Preflight	Maintain hydration
	Consider phase advance/delay techniques prior to departure[a]
	Maximize sleep to prevent preflight accumulation of sleep debt
In flight	Stay hydrated (avoidance of alcohol and caffeine is recommended)
	Immediate adjustment to destination meal[43] and light schedule[a]
	Attempt to follow destination sleep timing if possible (consider a short-acting sedative/hypnotic such as zaleplon[44])[a]
Post flight	Attempt to maintain destination sleep schedule[a]
	Judicious use of napping (≤ 15-30 min)
	Avoid operating vehicles for long periods during circadian nadir (home sleep period)
	Light therapy[a]
	Eastward travel—morning exposure to bright light; evening avoidance of bright light (consider short-wavelength sunglasses)
	Westward travel—evening exposure to bright light; morning avoidance of bright light (consider short-wavelength sunglasses)
	Melatonin administration[a]
	Eastward travel—melatonin 5 mg at destination bedtime (daily from day of departure until fully adapted)
	Westward travel—no melatonin administration recommended
	Consider sedative/hypnotic use (zolpidem, eszopiclone) at bedtime to assist with sleep initiation, if needed
	Consider caffeine use early in the day to combat sleepiness[44]

[a]These measures should only be used if phase-shift is desired at destination

most outcome variables (jet lag symptom scores), the inability to accurately quantitate circadian phase shift parameters in field experiments, and the soporific/hypnotic property of melatonin masking its circadian effects.[37] No major adverse effects are observed with exogenous melatonin used for short periods of time.[49] Light therapy has also been shown to be quite effective in shifting circadian phase in both easterly and westerly travel.[50,51]

Light therapy should be administered with natural outdoor light when available because of convenience for the traveler as well as the greater efficacy of phase shifting demonstrated with light of greater intensity,[52] although indoor light and commercially available light boxes may be used. An adjunctive therapy to light administration is the avoidance of light to prevent phase shifting in the undesired direction. The use of short wavelength (blue light) blocking glasses to prevent melatonin suppression at inopportune times is a promising therapy,[53] although further studies are needed before recommendations can be made. The combination of evening melatonin and morning bright light therapy are additive in their phase-advancing capacity and are beneficial for individuals traveling eastward.[47]

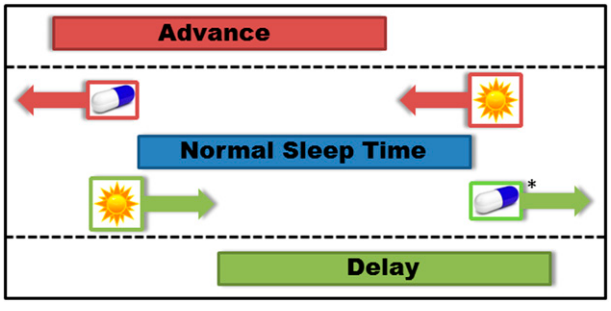

FIGURE 1. Schematic diagram of phase shifts due to light and melatonin administration. *Although demonstrated in the phase response curve for melatonin, it is unclear if melatonin administered in the morning hours clinically results in phase delay.

Recommendations for using melatonin and light therapy can be gleaned from the American Academy of Sleep Medicine practice parameters on circadian rhythm sleep disorders[54] and an understanding of the phase response curves previously described. For an individual flying eastward, in whom advancing the sleep phase is desired, melatonin administered at the desired time of bed along with early morning bright light exposure will assist with circadian shift. To blunt the acuity of jet lag symptoms, initiating therapy 3 days prior to travel along with advancing the normal bedtime (going to sleep an hour earlier for each of the 3 days) may be helpful. For westward travel, which is considered easier to adapt to because of endogenous circadian periodicity of >24 h, only bright light in the evening is recommended. The recommended dose of melatonin is 0.5 to 5 mg. The evidence does not provide clear suggestions regarding management of JLD in the setting of travel over many time zones (more than eight); in fact, several studies have demonstrated that individuals traveling over many time zones vary the direction of circadian adjustment, some advancing and others delaying their sleep phase.[55]

A method of preventing JLD is to maintain circadian alignment by maintaining a home sleep schedule in the destination location. Although most travelers are both unable and unwilling to do this because of their reasons for travel (ie, business or recreation), this strategy was shown to be effective in reducing symptoms of JLD in flight attendants during a two-night layover.[56] An alternative strategy is to initiate a shift in sleep schedule several days prior to travel, either

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Table 2—*Clinical Trials of Hypnotic/Sedative Use in Travelers*

Study	Year	No.	Drug	Duration	Travel Direction	Results
Zee et al[60]	2010	110	Ramelteon vs placebo	4 nights	East	Decreased sleep latency with ramelteon 1 mg vs placebo; variable effects on daytime functioning
Jamieson et al[61]	2001	138	Zolpidem vs placebo	3-4 nights	East	Zolpidem improved total sleep time and sleep quality and decreased awakenings
Reilly et al[62]	2001	17	Temazepam vs placebo	3 nights	West	Trend toward greater improvement in subjective jet lag scores with temazepam
Suhner et al[63]	2001	137	Zolpidem vs melatonin vs combination vs placebo	5 nights (including flight)	East	Zolpidem rated as most effective jet lag medication with subjective improvement in sleep quality and fewer jet lag symptoms; significant side effects of zolpidem
Buxton et al[64]	2000	6	Triazolam vs placebo	5 "nights"	West (simulated)	Improved circadian and homeostatic sleep measures with triazolam
Daurat et al[65]	2000	33	Zopiclone vs placebo	4 nights	West	Improved sleep duration and nocturnal activity scores with zopiclone; no difference in diurnal activity or subjective jet lag scores
Lavie[66]	1990	18	Midazolam vs placebo	4 nights	Both	Improved sleep duration/quality with midazolam on eastward travel only

alone or with light/melatonin therapy, such that preemptive circadian phase shift will assist with continued phase shift at the destination. Although this has not been formally studied, several melatonin trials included nightly doses of melatonin on each of three nights prior to travel.[57-59] When combined with a shift in the sleep schedule prior to travel, preflight melatonin dosing may decrease the time required for circadian realignment and improve symptoms.

Hypnotic medications have been used to improve sleep quality and reduce sleep onset latency with variable although generally good efficacy (Table 2).[60-66] Medications that have been evaluated include ramelteon,[60] zolpidem,[61,63] zopiclone,[65] and several benzodiazepines.[62,64,66] Although ramelteon (a melatonin agonist) has been evaluated for its hypnotic effect and is only approved by the US Food and Drug Administration for the treatment of insomnia, it and other melatonin agonists (tasimelteon and agomelatine) have shown chronobiotic properties[67] that may prove especially helpful in the treatment of JLD. Simulants, including caffeine and armodafinil, have likewise been studied and have demonstrated improved daytime alertness and function.[48,68-70] Although pharmacologic therapy does demonstrate a reduction in some symptoms of jet lag, pharmacokinetic profiles (unwanted prolonged sedation with hypnotics with longer half-lives) as well as other adverse effects of these medications must be considered prior to initiating therapy.

Conclusion

The clinical manifestations of sleep deprivation are well documented and include alterations in alertness and vigilance, mood and emotional state, memory processing, and executive function. Most travelers develop sleep deprivation both during the travel period and following arrival at their destination because of circadian misalignment and JLD. Further, the cognitive effects of the ensuing sleep deprivation likely result in the perpetuation of the general malaise that is a primary component of JLD. Although definitive treatment of JLD is not available, strategies discussed in this review, including appropriately timed administration of bright light therapy and melatonin, planned sleep scheduling, and possibly pharmacologic therapy, should diminish symptoms and enable individuals to accomplish their specific goals during their travels.

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