

SLEEP LOSS AND SLEEPINESS: PHYSIOLOGICAL AND NEUROBEHAVIORAL EFFECTS

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The effects of sleep loss and sleepiness encompass a variety of neurobehavioral and physiologic alterations. This chapter reviews the causes, consequences, and mechanisms of sleep disruption and concomitant daytime sequelae, namely sleepiness and neurobehavioral performance decrements. Given the personal distress, quality of life issues, public health concerns, and economic costs of sleep loss and sleepiness, it is imperative that researchers and practitioners strive to obtain a solid understanding of these consequences and mechanisms. Several advances in the psychopharmacologic and behavioral treatments of the causes and consequences of sleep loss have recently evolved. Technologies are rapidly developing and showing promise for effective evaluation of these highly prevalent problems.

Advances and online monitoring and mathematical modeling of sleepiness and associated neurobehavioral forms are rapidly evolving novel behavioral and psychopharmacologic treatments effective for the causes and consequences of sleep loss.

PATHOPHYSIOLOGY OF DIFFICULTY INITIATING OR MAINTAINING SLEEP

Insomnia is characterized by difficulty initiating or maintaining sleep that results in psychological distress and impaired social or occupational functioning (1). Individuals with insomnia report a myriad of interpersonal, cognitive, affective, behavioral, and physical symptoms. Not only are there consequences for the individual, but also are there

substantial costs to society; the direct economic costs owing to insomnia are estimated at \$13.9 billion (2). The etiology of these symptoms has not been clearly delineated, however. The causal explanation that sleep deprivation accounts for the impairment of daytime functioning in insomniacs has been challenged and needs re-evaluation. This section provides a review of the daytime sequelae of the insomnia and a discussion of alternative mechanisms that may account for the daytime symptoms experienced.

Consequences

Persons with insomnia report various somatic complaints and demonstrate increased health-seeking behaviors. The primary complaints among insomniacs include drowsiness and tiredness on awakening, as well as sleepiness throughout the day (3,4). Insomniacs complain of physical ailments such as headache, diarrhea, stomach discomfort, heart palpitations, pain, tiredness, and weakness more frequently than do controls (5). Health-seeking behaviors such as hospital and physician visits are more frequent among a clinical sample of insomniacs compared to controls (5). Cardiovascular disease (6) and decreased immune functioning (7) may also be exacerbated in chronic insomnia.

The quality of life among insomniacs also appears to be diminished (8). Absenteeism, and work and social limitations are significantly more prevalent among insomniacs compared to normal sleepers (5,8). Insomniacs report restricted physical activities, poorer health, less vitality, and a decreased amount of time spent reading and engaging in recreational activities (8). Insomniacs report more time watching television, relaxing, and shopping than do noninsomniacs, whereas non-insomniacs work more, study more, and socialize more than do insomniacs. Insomnia is also associated with dissatisfaction in interpersonal relationships (4). These data suggest that insomniacs avoid or are unable

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to participate in activities that require higher levels of concentration or social engagement.

Insomnia and mood disturbances often coexist. Sleep disruption is the single most common complaint of patients in a major depressive episode (9). Likewise, 30% of patients who complain of insomnia have a concurrent depressive disorder. Some have speculated that chronic insomnia may contribute to the development of major depressions (10, 11); however, prospective controlled studies are needed to test these speculations. Kales and associates (5) found that insomniacs also exhibited symptoms mood changes, such as dysphoric mood, worry, tension, anxiety, and irritability. Even in nonclinical samples, insomniacs reported decreased mood (4), increased anxiety and depression, and less optimism (8). In contrast, Marchini and associates (12) reported that insomniacs were not particularly ruminative, tense, or physiologically aroused, but rather passive and calm. Marchini and colleagues' (12) unexpected finding led them to hypothesize that there may be different types of insomniacs: (a) hypoactive, as described; and (b) hyperactive, who are more anxious. They also suggested that insomniacs might be hypoactive during the day and hyperactive at night.

The causal direction of the relationship between insomnia and mood disorders is not clearly established. We cannot readily assume that psychiatric symptoms are merely sequelae of insomnia, nor can we definitively assume that insomnia is always a consequence of psychopathology. Clearly, we need to attend to the relationship between mood and insomnia. Even if criteria for a diagnostic disorder are not met, the interplay between moods and insomnia need to be examined in order to increase our knowledge of the etiology and guide treatment efforts.

Insomniacs' primary cognitive symptoms are impaired concentration and memory difficulties (4). Compared to noninsomniacs, insomniacs also rate their attention, memory, reasoning, problem-solving, and reaction time more poorly. Although there is some evidence that insomniacs have difficulty with semantic memory (13), reaction time, and digit span (14), objective verification of performance deficits have not consistently corroborated these subjective performance complaints. Interestingly, Sugerman and associates (15) showed that subjective insomniacs (no PSG corroboration), in contrast to objective insomniacs (PSG corroboration), displayed cognitive deficits. Thus, there may be factors other than sleep loss that account for these reported decrements. First, these data lead one to question whether or not insomniacs are indeed sleep deprived; and second, to hypothesize what could account for these reported symptoms if not sleep deprivation.

Are Insomniacs Sleep Deprived?

Daytime symptoms may not solely be attributable to sleep loss. First, for the majority of insomniacs it is questionable

whether they suffer significant sleep loss compared to "good sleepers." Insomniacs have a tendency to overestimate their sleep latency, that is, the time from lights out to the onset of electrophysiologically defined sleep, and underestimate total sleep time (16). Although some insomniacs, particularly those with corroborating PSGs, demonstrate compromised sleep efficiencies and intermittent waking time (13), it is not clear that sleep is significantly disparate from that of noncomplaining sleepers in the majority of insomniacs.

Second, studies consistently find that insomniacs do not demonstrate daytime sleepiness, as measured by the Multiple Sleep Latency Test (MSLT) which measures sleep onset time when an individual is given an opportunity to sleep during the day (17,18). In fact, Stepanski and associates (18) found that insomniacs were less sleepy than good sleepers, based on the results of the MSLT. These results must be interpreted with strong caution, however. The MSLT measures sleepiness and ability to fall asleep. Inability to initiate sleep may be a characteristic of insomniacs both during the day and night. Thus, an insomniac may feel sleepy, but not be able to sleep during an MSLT; the results would then artificially underestimate the level of sleepiness. This measure is of dubious utility in the evaluation of sleepiness in those who cannot initiate sleep.

To circumvent this measurement difficulty, Lichstein and colleagues have used an index of sleepiness that does not depend on sleep ability, but rather diameter of the pupil as a measure of sleepiness. Although there is some evidence to suggest that insomniacs differ from noninsomniacs on sleepiness as measured by pupillometry (19,20), the effects were marginal. The technique may be promising, but the results are inconclusive.

Third, neither the quality nor quantity of nighttime sleep predicts the next day's functioning. One would expect that a worsening of nighttime sleep would exacerbate daytime impairment. Measures of sleep efficiency (17), total sleep time (TST), and polysomnographic (PSG) recordings (13, 15,20) do not always directly relate to measures of daytime functioning. In fact, TST was correlated with increased tendency for drowsiness (17) and better nighttime sleep was correlated with increased sleep tendency during the day, for both insomniacs and noninsomniacs. Bonnet and Arand (21) also demonstrated that a worsening in sleep was not related to worsened daytime functioning. What, then, could account for the decrements in daytime functioning?

Hypothesized Mechanisms

Several studies support the notion that insomniacs are not necessarily sleep deprived; rather, they are hyperaroused and thus unable to fall asleep (17,18,21,22). This chronic activation may account for the inability to fall asleep at night and during the day, as measured by the MSLT (18). Bonnet and Arand (22) "yoked" the sleep of controls to that of insomniacs. Despite sleeping similar amounts, normal

sleepers exhibited a pattern resembling a sleep-deprived state (decreased tension and vigor, body temperature, and MSLT latencies). Insomniacs demonstrated a pattern of hyperarousal inconsistent with sleep deprivation (increased metabolic rate, body temperature, tension, and decreased vigor); therefore, daytime symptoms may be the result of hyperarousal, not sleep deprivation.

As alluded to in the preceding, perhaps psychopathology, either at the clinical or subclinical level, may account for both insomnia and daytime symptoms. For example, anxiety could account for sleep onset difficulties at night and symptoms of fatigue during the day (23). Likewise, Coyle (24) found that insomniacs with negative affect perceived impaired daytime cognitive functioning and motivation, whereas insomniacs with positive affect perceived better cognitive and motivational functioning.

How an insomniac reacts to his or her sleep disruption may also predict his or her experience of daytime functioning. Several hypotheses related to this notion are offered. Insomniacs may also be “short sleepers,” believe that their sleep is insufficient, and consequently become distressed about it during the day (20,25). Insomniacs simply may need more sleep than they are getting or be hypersensitive to small amounts of sleep loss (17). Consistent with these hypotheses, Dorsey and Bootzin (26) examined subgroups of insomniacs classified as objective insomniacs (OI) and subjective insomniacs (SI), with or without corroborating objective sleep disturbances, respectively. Like other studies, differences in performance, alertness, and night sleep parameters were not evidenced. SIs inaccurately estimated sleep/wake state in comparison to objective measures on the MSLT. OIs were more introverted, more withdrawn, and more able to accurately describe the amount of sleep that they had, but were perhaps too internally focused; SIs seemed to be more neurotic and unaware of their internal conscious state. These data suggest that the complaints of insomniacs may be differentiated and better understood by way of personality subtypes.

Studies of physiologic changes accompanying insomnia have produced inconsistent and generally unreplicable findings. The inconsistency may well derive from the heterogeneous samples from the different studies. In fact, the heterogeneity of all those diagnosed with “insomnia” confounds most studies in this field (27).

PATHOPHYSIOLOGY OF DISORDERS OF EXCESSIVE SOMNOLENCE

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) afflicts up to 4% of middle-aged adults and is characterized by respiratory pauses owing to upper airway closure during sleep, which result in acute hypoxemic events and transient arousals from sleep. Individuals with OSA primarily complain of daytime somnolence,

yet are often completely unaware of their loud snoring, apneic and hypopneic events, and sleep fragmentation. Daytime performance is markedly impaired. Studies demonstrate impaired vigilance, reduced reaction times, daytime microsleeps, memory impairment, and depressive symptoms (28–30). Findley and associates (31) found that persons with apnea had poorer performance on “Steer Clear”—a 30-minute computer-generated visual vigilance driving simulation task that measures sustained attention and simple reaction times—than did age-matched control participants. The outcomes of these problems include impairment in work efficiency, increased automobile accident rates, and decrements in quality of life. In the case of truck drivers, pilots, and other operators of heavy machinery, these consequences of sleep-disordered breathing can be catastrophic.

Maintenance of respiration during sleep is dependent on intact central nervous system centers controlling respiration, respiratory reflexes, respiratory musculature, and innervation of the diaphragm and intercostal muscles, as well as a patent upper airway (32). The emphasis of clinical and research approaches to sleep-disordered breathing has focused on this last point—loss of airway patency. Two classes make up most of the obstructive sleep apnea patients. The majority of patients with OSA are obese and have short, thick necks with reduced upper airway diameters owing to excess tissue. A smaller proportion of patients are of normal weight, but are also prone to closure of the upper respiratory tract. These latter individuals typically have oral or maxillofacial structural changes resulting in congenitally small airways. Sleep produces a loss of postural tone of upper airway structures (32) that contributes to the onset of apneic events. Arousals from sleep, owing to combined hypoxemia and hypercapnia, are initiated to restore airway patency (33). Depression of arousal from acute or chronic sleep loss, alcohol, or other sedating drugs increases the propensity for apneic events. Thus, as apneics undergo chronic sleep loss from the repeated arousals, the daytime sequelae progress over time. It remains unclear which elements of OSA are responsible for the hypersomnolence and impaired neurobehavioral performance—repeated arousals from sleep or sleep hypoxemia (34).

Narcolepsy

Narcolepsy, with an estimated prevalence of about 50/100,000 (35), is a disabling disorder that may result in more daytime somnolence than any other major sleep disorder. In addition to the daytime somnolence, it is characterized by cataplexy, rapid switches from waking to sleeping states, sleep paralysis, and hypnagogic hallucinations (36). Not only do patients feel drowsy, but also they rapidly switch from waking to sleeping or cataplectic states—the sudden loss of all skeletal muscle control. This combination of severe excessive daytime somnolence coupled with sleep at-

tacks makes them particularly prone to impaired daytime neurobehavioral performance. Decrements in performance, including vigilance, and attentional and complex cognitive functioning problems, may be direct consequences of sleepiness (37). In the Findley and associates study, persons with narcolepsy demonstrated marked impairments as the duration of the task increased, with shorter latencies on the MSLT predicting greater performance errors. In addition, 20% to 30% of narcoleptics have comorbid major depressive episodes (38,39), although the reasons for this relationship remain largely unexplored.

Until recently, altered cholinergic and monoaminergic systems have been implicated in the pathophysiology of this disorder (40); however, new work from canine strains with narcolepsy, and a strain of Orexin knockout mice (manifesting a phenotype highly similar to narcolepsy) reveals that a genetic defect, disruption of a hypocretin (Orexin) gene may be the primary cause of narcolepsy (41,42). Orexins are a class of hypothalamically derived peptides with known effects on appetite and feeding behavior; however, until recently they were not recognized as sleep-modulating neurotransmitters.

Restless Legs Syndrome and Periodic Limb Movements in Sleep

Restless legs syndrome (RLS), a sleep-related disorder with an estimated prevalence of 1% to 5%, is characterized by unpleasant sensations experienced predominantly in the legs, which occur only at rest and become more pronounced in the evening or at night. Patients suffer from an urge to move their legs, often counteracted by walking, which leads to partial, temporary relief of the sensations. Most patients with RLS have periodic limb movements during sleep (PLMS) characterized by repetitive abrupt, involuntary flexion of the extremities that results in brief arousals and repeated complete awakenings. PLMS can occur as an isolated phenomenon, but often occurs with other sleep disorders, including RLS, narcolepsy, sleep apnea syndrome, or REM sleep behavior disorder.

The etiology of RLS and PLMS is unknown. It is hypothesized that PLMS results from a disinhibition of descending inhibitory pathways. Disturbances in dopaminergic, adrenergic, and opiate systems may contribute to RLS/PLMS (43); however, the evidence that these systems are responsible for the pathophysiology is inferentially derived from the fact that pharmacologic agents modulating these systems confer some clinical benefit. Daytime performance impairments that appear secondary to the sleep disruption have been poorly studied.

NEUROBEHAVIORAL AND PHYSIOLOGIC EFFECTS OF SLEEP LOSS

The evaluation of sleepiness is critical not only to minimize impairment in social or occupational settings, but also to

ensure safety. Consequences of sleepiness and fatigue can lead to a myriad of neurobehavioral performance decrements and potentially dangerous situations, such as traffic and work accidents. The following section outlines the primary public health concerns and the populations that are most vulnerable to the consequences of sleepiness and fatigue, such as travelers, truck drivers, and shift workers. In addition, neurobehavioral consequences of experimentally induced sleep loss are reviewed.

Traffic Accidents

According to the National Highway Traffic Safety Administration, 56,000 automobile accidents per year are caused by drivers falling asleep at the wheel (44). Accidents involving truck drivers result in approximately 4,800 fatalities per year (45) and fatigue is the most common cause (46). Sleep-related automobile accidents are associated with fatalities (1.4%) comparable to those of alcohol-related crashes (2.1%) (47). Drowsiness can lead to rapid and frequent uncontrolled sleep or microsleeps, frequent prolonged eyelid closures, and inattention in the form of behavioral lapses that involve a failure to detect a monitored stimulus or a failure to respond in a normal timely manner (48).

Several factors are predictive of fatigue-related traffic accidents. Having an untreated sleep disorder such as insomnia, narcolepsy, or sleep apnea significantly increases the risk of having a motor vehicle accident (MVA) (49,50). The amount of sleep truck drivers obtain during the sleep episode prior to the accident inversely predicts the likelihood of an MVA (46). The homeostatic need for sleep and the circadian pacemaker interact in predicting performance in a dynamic, nonlinear fashion (51). Consistent with our knowledge of sleepiness and circadian neurobiology, midafternoon (approximately 3 PM) and nighttime hours (12 AM to 7 AM) are times when both sleepiness is increased and accidents are most likely to occur. Young drivers (under 45 years) are more likely to be involved in an accident during the night, individuals aged 45 to 65 are more likely to be involved in an accident around 7 AM; elderly drivers' peak accident time is at 3 PM.

Shift Workers

As many as 25% of employed individuals engage in shift work—employment outside the typical 7 AM to 7 PM workday—that can have severe personal and public health consequences. Sleepiness is reported by 70% of shift workers (52). Although it is difficult to discern the exact effects of sleepiness on daytime functioning, problem sleepiness among shift workers is associated with decreased quality of life (53), decreased productivity (54), and gastrointestinal and cardiovascular disease (55). Shift workers have a higher incidence of traffic accidents as a result of sleepiness while commuting, compared to non-shift working individuals (56). Shift

workers are also at an increased risk for injury and accidents (51). Three Mile Island, Exxon Valdez, and the Space Shuttle Challenger represent disasters where fatigue among nighttime workers has been implicated.

Both intrinsic biological and environmental factors contribute to the problem sleepiness of shift workers. Compared to individuals engaged in regular hour employment, shift workers sleep approximately 2 hours less per 24-hour sleep cycle as measured by EEG studies (57). Shift workers exist in states of chronic sleep debt because of insufficient sleep during each 24-hour period. Human entrainment to the natural 24-hour light/dark cycle establishes a fixed neurobiologic propensity to be active, alert, and performing during the daylight hours, and to sleep during the nocturne (58). Shift work requires maximum psychomotor and cognitive performance at night, that time when virtually all zeitgebers are cueing the endogenous circadian pacemaker to reduce arousal, activity, and sleep. Thus, not only must shift workers compensate for societal disruptions to their sleep, such as noise and pressures to socialize and perform domestic chores, but they must also overcome daylight and darkness time cues to work and sleep, respectively (53).

Jet Lag

Jet lag is a condition following transmeridian travel that involves a myriad of problems. Symptoms include daytime sleepiness and fatigue, impaired daytime cognitive performance, poor psychomotor coordination, dysphoric mood, and difficulty falling asleep according to the new schedule. The time needed to resynchronize to the new local light/dark cycle increases with the number of time zones crossed.

Like those of shift work, the adverse consequences of jet lag are mediated by disruptions of the sleep and circadian systems. Both the homeostatic mechanism for sleep (sleep drive that increases as duration of wakefulness increases) and circadian neurobiology interact to determine neurobehavioral alertness and performance (59). Jet lag-induced neurobehavioral performance decrements are primarily accounted for by the phase discrepancy between the organism's endogenous circadian rhythms and the new, local 24-hour light/dark cycle, although sleep loss incurred by travel can also serve to exacerbate the condition. The endogenous circadian pacemaker does not immediately adapt to the new light/dark cues, but rather requires a period for resynchronization or re-entrainment occurs during which individuals are likely to experience fatigue and performance deficits. An individual traveling eastward to a destination with a 9-hour time difference may feel compelled to sleep at 9 PM (home time) because of circadian propensity and increased homeostatic sleep drive. However, zeitgebers in the new destination (6 AM) associated with wakefulness, such as sunlight, are discrepant with the individual's endogenous pacemaker and the homeostatic sleep drive associated with sleepiness.

Sleep Deprivation: Experimentally Induced

Sleep loss results in compromised neurobehavioral performance and neurophysiologic functioning (60). Various performance assessments probe the functional capability of the CNS and offer meaning to the physiologic changes that occur as a result of sleep loss (61). Numerous studies show that as sleeplessness increases, so do subjective and objective measures of sleepiness and neurobehavioral problems. Psychomotor vigilance and probed memory impairment as well as somatic complaints appear to increase during acute total and repeated partial sleep deprivation (62–65). Some studies have been unable to show cognitive impairment during sleep deprivation (66), leading to speculation that chronic partial sleep deprivation does not result in cumulative decreases in performance (67,68). A number of factors may have contributed to the disparate outcomes among studies of waking performance after chronic sleep restriction. Many of the negative studies were limited by the fact that the primary outcome measures were performance assessments with robust practice effects (62). Learning curves confound cumulative performance deficit measurements; therefore, they compromise the validity of conclusions concerning the lack of such effects. In other words, repeated testing on a measure with a learning curve will lead to improved performance scores. Thus, if cumulative sleep loss does impair performance on this measure, the decrement will be masked by the learning-derived improvement.

Demonstration of cumulative performance deficits requires utilizing measures that are both sensitive to the effects of sleep loss and have no learning curve. Performance vigilance tasks, cognitive throughput tasks, and tasks requiring rapid response shifts incorporate both of these criteria. Studies utilizing such measures show increased lapses and heightened variability of performance during sustained vigilance tasks (62), all of which show deterioration after acute, total sleep deprivation, and after chronic partial sleep deprivation. During sleep loss, increased rates of slowing in response time result in accelerated decline in average performance with increasing task duration, independent of lapsing. Reduction in speed of response, although not a function of lapses or failure to respond, appear attributable to a decline in the ability to continuously allocate attention to the task and to respond motorically as rapidly as possible. The increase in false response rates or errors of commission, increase during chronic partial sleep deprivation, demonstrating that increased compensatory effort and a loss of motivation cannot account for these neurobehavioral performance decrements.

The magnitude of sleepiness on performance is a result of the dynamic influences of duration awake and underlying circadian rhythms. Motivation and incentive can contribute to, or override, the sleep-induced impairments, but only for a limited time. Sleepiness, fatigue, stress, and impaired

vigilance during sustained sleep restriction accumulate over time (62). Studies suggest that performance degrades in a dose–response manner (69). Kuo found that during chronic partial sleep deprivation, subjective sleepiness increased during the first week, but decreased during the second week (70), suggesting that subjects believed they were adapting to the effects of sleep loss, whereas performance measures indicated that they were not. Subjects were unaware of their neurocognitive dysfunction, because they “felt fine.”

Neurophysiologic functioning is altered during total sleep deprivation of 24 to 48 hours (TSD). (See ref. 60 for review.) Cumulative sleep loss produces decreased latency from wake to sleep onset, microsleep intrusions into wakeful periods, and involuntary sleep onsets. Constricted pupil size, difficulty with balance and coordination, and undulating slow eye movements are also observed as result of TSD. Prolonged sleep loss produces a modest dopaminergic and adrenergic activation, elevated levels of TSH, T3, and T4, hyperactivity of some immune parameters, and hypothermia. Remarkably, the hypothalamic-pituitary-adrenal axis (the “stress” axis) remains largely unaffected by sleep loss. Although recovery from TSD is marked by increased sleep intensity, sleep loss does not produce irreparable harm; changes can be reversed with recovery sleep.

Sleep deprivation in healthy individuals tends to produce little, if any, worsening of mood, anxiety, or anger, but does produce worsening self-reports of fatigue, vigor, and confusion. In contrast, depressed patients demonstrate increased locomotor activity, increased self-ratings of vigor, reduced fatigue, and improved mood after approximately 30 hours of sleep deprivation (71,72). This seemingly paradoxical effect in depressed individuals may reflect an underlying heightened sensitivity to the sleep deprivation-induced increases in dopamine, hypothalamic-pituitary-thyroid axis activity (73). Studies aimed at understanding these opposite effects in depressed and healthy persons to elucidate mechanisms are needed.

TREATMENT FOR SLEEP LOSS AND SLEEPINESS

Insomnia

Results from recent metaanalyses indicate that nonpharmacologic treatments for chronic insomnia are effective for the majority (70% to 80%) of patients (74) in reducing latency to sleep onset and wake after sleep onset by approximately 50% (e.g., to approximately 30 minutes). Effective treatments for insomnia include stimulus control (75), progressive muscle relaxation (76), paradoxical intention, sleep restriction (77), biofeedback (78), and cognitive therapy (79). (See ref. 27 for a further description of nonpharmacologic treatments.) Although the benefits of using combined pharmacologic and nonpharmacologic treatments has not been investigated extensively, some data suggest that behavior

therapy alone, pharmacotherapy alone, and the two in combination provide comparable efficacy in the short term, but behavioral approaches may excel in the long term. (See ref. 74 for a review.)

Although patients have reported sleep quality improvement by using these strategies, the degree to which daytime sequelae, such as self-reported cognitive impairment, mood disturbance, and quality of life, remit has not yet clearly been determined. This is particularly relevant given the hypothesis that it may not be sleep loss per se that accounts for daytime impairment, but rather concomitants such as hyperarousal, cognitive distortions, and distressed mood that account for daytime performance and functioning. Strategies such as cognitive-behavioral therapy and progressive relaxation hold promise for managing these noted daytime sequelae.

The classic benzodiazepines and the newer, more selective benzodiazepine agonists zaleplon and zolpidem are extremely effective at inducing and sustaining sleep. The role of these compounds in treating insomnia is described in greater detail elsewhere in this text. Many of them unfortunately also produce residual daytime somnolence and impaired neurobehavioral performance. Typically, the longer-acting agents are more likely associated with these adverse effects. The newer agents, zaleplon and zolpidem, appear to produce less daytime problems than the older agents (80), however, whether any of these compounds reverse the daytime impairments to which insomniacs are prone remains to be seen.

Additional research is needed to assess the effects of pharmacologic and nonpharmacologic treatments not only for sleep quality (total sleep time, wake after sleep onset, sleep efficiency), but also for daytime performance, function, and distress.

Excessive Somnolence

Daytime napping is a behavioral strategy commonly used to alleviate excessive somnolence and enhance alertness in everyday life. The efficacy of napping, however, is contingent on the causes of the sleepiness and performance deficits. For whom and under what conditions is napping effective at alleviating sleep and enhancing alertness? The propensity for adults to nap in the midafternoon is relatively consistent across all cultures and appears tied to the endogenous circadian system. Some cultures, such as those in Mexico, China, or Greece, endorse taking afternoon siestas, consistent with the chronobiologic tendency. Perhaps owing to industrialization or occupational demands, other countries (e.g., the United States and Japan) do not endorse this practice, despite the endogenous drive for sleep in the midafternoon. Thus, napping is a behavior that is consistent with the circadian rhythm dip in the midafternoon and can be used to enhance functioning, even for individuals who do not exhibit sleep disorders (81).

For individuals with sleep disorders, however, the usefulness of napping in alleviating symptoms depends on the nature of the dysfunction (i.e., the underlying mechanism that contributes to the symptoms) (81). One might assume that napping is a healthy way of managing excessive somnolence regardless of the underlying mechanism. Many persons with narcolepsy find brief daytime napping to be helpful, whereas persons with untreated sleep apnea derive no benefit from napping (81). Napping improves reaction time performance in individuals with narcolepsy-cataplexy (82). Likewise, the strategy of “prophylactic napping” in advance to prevent anticipated sleepiness is quite helpful for individuals (e.g., truck drivers or shift workers) who need to work for prolonged hours (83). Appropriately timed napping can be beneficial for treatment of jet lag in some circumstances (84).

Two caveats are described regarding the use of napping for managing excessive somnolence. First, side effects of napping can include sleep inertia, which is characterized by sleepiness, diminished alertness, and reduced performance that occurs immediately on waking from sleep but that dissipates within 1 to 4 hours of awakening (85–87). Sleep inertia can be especially problematic for those who need to perform immediately on awakening. Second, if a nap is too long, it can interfere with nighttime sleep. Hence, napping is not recommended for individuals whose primary presenting problems directly involve difficulty initiating or maintaining nocturnal sleep.

Wake-Promoting Compounds

Caffeine is the most widely used wake-promoting compound in the world, most often consumed in high, intermittent dosages (150 to 300 mg) and usually in the hours just after awakening. Caffeine is most often used to counter the effects of morning sleep inertia. However, some also use it throughout the day to maintain wakefulness. This may be a natural countermeasure to daytime sleepiness caused by insufficient sleep the prior night. Research is needed in this area. Caffeine is a safe and simple wake-promoter that has been “staring us in the face,” but little research has focused on how to use caffeine as a practical and safe wake-promoter in the context of daytime sleepiness.

The mechanisms by which caffeine is able to promote wakefulness have not been fully elucidated (88). Most studies indicate that, at the levels reached during normal consumption, caffeine exerts its action through antagonism of central adenosine receptors (89,90). It reduces physiologic sleepiness (91–93) and enhances vigilance and cognitive performance (94,95). These beneficial effects have also been reported for caffeine taken during sleep deprivation (91,93,94).

Classical psychomotor stimulants such as methamphetamine and methylphenidate are potent centrally active compounds with central and peripheral sympathomimetic activ-

ity. In contrast to caffeine, methamphetamine and methylphenidate produce neurobehavioral activation and promote wakefulness by increasing dopaminergic and noreadrenergic neurotransmission. These compounds have a number of potentially undesirable side effects, including anxiety, appetite suppression, tolerance, dependence, and abuse potential (96).

Modafinil is the first of a new class of wake promoting therapeutics (97,98). The mechanism(s) by which it improves alertness and vigilance and reduces sleepiness remains obscure. Some work suggests that modafinil may promote activity at α 1- and β -adrenergic receptors (99) and 5-HT₂ receptors (100). Its ability to stimulate dopaminergic activity remains controversial. New work has demonstrated that it actually stimulates Orexin-containing neurons in the hypothalamus of mice (42). Unlike amphetamines, modafinil does not appear to produce dependence or have addictive potential (98,101). The novel wake-promoting compounds hold potential for enhancing understanding of the mechanisms of pathologic somnolence and for the treatment of the disorders of excessive sleepiness.

Obstructive Sleep Apnea

Treatments for OSA are directed at maintaining airway patency and thereby preventing the apneic events. The most effective methods developed to date include continuous positive airway pressure (CPAP), weight loss, dental appliances that reposition the jaw and/or tongue, and surgical procedures. These treatments have been demonstrated to improve the daytime somnolence, impaired vigilance, depression, and overall quality of life (28–30). Few randomized, well-controlled trials have been published that evaluate pharmacologic agents in the treatment of obstructive sleep apnea. Respiratory stimulants (theophylline), psychostimulants, adrenergic agonists, opioid antagonists, and nicotinic agents, have been studied with mixed results. Non-OSA sleep-related breathing disorders such as hypercapnic obesity-hypoventilation, myxedema, central apnea, and periodic breathing in congestive heart failure respond to specific pharmacologic measures. Future research including the use of the newer wake-promoting compounds, such as modafinil, is warranted.

Narcolepsy

Until recently, standard treatments for narcolepsy often included a combination of amphetamine-like stimulants for sleepiness and antidepressant therapy for abnormal rapid eye movement sleep events (cataplexy, sleep paralysis, and hypnagogic hallucinations). These treatments are purely symptomatically directed and involve activation of central dopaminergic and adrenergic systems (36). Modafinil is the first specific treatment approved in the United States for treatment of narcolepsy. With the discovery of the genetic

markers for narcolepsy, even more novel approaches appear conceivable. Gene therapy or compounds affecting Orexin, systems one of which is modafinil, are likely directions for future research.

RLS/PLMS

Treatment of RLS/PLMS is targeted toward dopaminergic, adrenergic, GABA, and opiate systems. L-Dopa, dopamine agonists, benzodiazepines, opioids, clonidine, and carbamazepine appear effective. With no obvious cause, treatment has been aimed at symptom control to date (43).

Shift Work and Jet Lag

The disturbances in circadian neurobiology associated with shift work and jet lag appear to be responsive to interventions that alter the underlying circadian system. Bright light therapy and exogenously administered melatonin are potent zeitgebers capable of inducing phase shifts in humans. Regulation of exposure to sunlight and artificial light (102,103), napping (104), caffeine to promote alertness at night and hypnotics to help daytime sleep (105), and melatonin to adjust circadian rhythms (106,107) are all helpful in limited studies. This evidence is in need of replication and application to other real-world situations.

RECENT ADVANCES IN ASSESSMENT AND PREVENTION TECHNOLOGIES

As discussed, the MSLT and pupillometry aid in the assessment of sleepiness. Wrist-worn actigraphic devices that monitor locomotion have demonstrated utility in monitoring sleep-wake patterns and sleep quality as well as assessing sleep disorders. (See refs. 108 and 109 for review.) A newly introduced technology, the sleep switch, is a handheld instrument that effectively detects latency to sleep onset (110). The patient presses and holds a button. When the patient lapses into sleep, voluntary motor tone is lost, the button is released, and an event marker notes the time. Unlike actigraphy, it cannot measure total sleep time; however, it has the distinct advantage as an objective estimate of sleep onset latencies for measuring insomnia, compared to actigraphs and compared to the subjective estimates of sleep logs that have traditionally been used (110).

The development and validation of technologies to detect and monitor fatigue is essential (111). As discussed, fatigue-related motor vehicle crashes and performance errors owing to sleep loss are pervasive and individuals are unreliable predictors of their own level of impairment (70,112). Moreover, current standards of proscriptive hours are not sufficient at preventing crashes, even when compliance is 100%. Thus, technology offers advantages of both objective verification of sleepiness levels and a viable alternative to

enhance and improve safety while facilitating occupational and economic goals.

Four major categories comprise operator-centered fatigue monitoring technologies. First, readiness-to-perform and fitness-for-duty technologies for drowsiness—aim to measure the functional capacity for work to be performed. Some measure fatigue by physiologic fitness (pupil or ocular scanning), whereas others measure performance via a battery of simple performance tests (113). Second, mathematical models of alertness are combined with ambulatory technologies to predict fatigue (114–116). These typically involve a device, such as an actigraph, which measures fatigue in combination with a formula (mathematical model) that predicts performance capacity for a given period of time when sleepiness is likely to occur. Third, vehicle based performance technologies focus on the vehicle, in contrast to the driver (117–120). They are designed to monitor the vehicle hardware systems that are subject to the alterations of the driver's performance, such as steering or speed variability or lane swaying. Fourth, in-vehicle, on-line, operator status monitoring technologies aim to monitor biobehavioral features of the operator (e.g., eyes, face, head, heart, brain electrical activity) on-line. Example of devices include: (a) video of the face, which monitors the eyelid position, blinks, movements, head nodding, direction of gaze; (b) eye trackers; (c) wearable eyelid monitors; (d) head movement detectors; (e) EEG algorithms; and (f) ECG algorithms (111). All these systems have relative merits and drawbacks. Clearly the status of these technologies is promising.

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