Measuring Treatment Efficacy in Insomnia

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The measurement of insomnia treatment efficacy has evolved over time. Historically, patient report measures were used to assess sleep the previous night, and, although important, these measures were not objectively validated. While the advent of polysomnography complemented patient reports of nocturnal sleep, few studies have evaluated daytime functioning and impact of impaired sleep on comorbid medical and psychiatric illnesses as measures of the efficacy of hypnotics. In the future, therapeutic endpoints will focus on important factors associated with insomnia, such as enhanced alertness, improved outcomes associated with augmentation therapy for depression, reduction in pain severity, and decreased sleep disturbances associated with hot flashes.

(J Clin Psychiatry 2004;65[suppl 8]:8–12)

Hypnotic agents have traditionally been used to treat specific insomnia symptoms such as difficulty falling asleep and waking during the night (termed *sleep onset* and *sleep maintenance*, respectively). Specific measures of these parameters evolved so that efficacy could be evaluated. Measurements of improvements in insomnia symptoms were initially based on patient report and, although useful, were not objectively validated. More recently, polysomnographic measurements of drug efficacy have been utilized. These allow for objective determination of the efficacy of an anti-insomnia agent. Over time, additional measures have been used in drug efficacy studies, such as sleep quality; sleep continuity, which is not well studied and has not been systematically measured; and sleep stages, which are not true efficacy measures.

The characteristics of individual hypnotic agents have traditionally influenced what measures of efficacy are emphasized. Historically, longer-acting drugs such as flurazepam demonstrated sleep induction and sleep maintenance efficacy in the face of significant residual daytime effects,[1–3] and so sleep maintenance measures, such as wake time after sleep onset and number of awakenings, were emphasized. More recently, the evolution of shorter-acting agents has resulted in an emphasis on the absence of residual effects, and reduced sleep latency, at the cost of sleep maintenance.[4,5] Questions arise regarding the use of these measures when one considers how few of them have been evaluated as determinants of improved *outcomes* in insomnia. Improvements in related morbidity are particularly important given that insomnia occurs so commonly as a comorbid condition and influences the course of many illnesses.

This article will elucidate which measures have been evaluated to be true determinants of improvement in insomnia-related impairment and will discuss possible future directions for insomnia measurements as they relate to functional improvement.

DETERMINANTS OF INSOMNIA-RELATED IMPAIRMENT

Parameters currently used to determine insomnia treatment efficacy include those associated with sleep induction,[4–6] sleep maintenance,[1,2,4] total sleep time (TST),[7,8] sleep efficiency,[4,9] sleep continuity,[10,11] sleep quality,[5,12] and sleep stages.[2,13] However, these parameters have not been studied with regard to improved daytime consequences or better outcomes in insomnia.

Sleep induction and sleep maintenance parameters are important for diagnosing insomnia; however, in the absence of a decreased TST (duration of sleep), they have not been shown to be associated with insomnia consequences. Sleep efficiency—defined as the ratio of total sleep time to time in bed, an important determinant of sleep hygiene—has also not been demonstrated to be associated with daytime consequences. On the other hand, both sleep continuity (uninterrupted sleep) and TST have been related to consequences of insomnia that potentially demonstrate their importance as measures of treatment efficacy.

Correlates of Impaired Total Sleep Time

TST has been associated with impaired alertness,[14] impaired performance,[15] impaired memory,[15] increased risk of car accidents[16] due to sleepiness, reduced pain threshold,[17] and insulin resistance.[18]

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Support was provided through an unrestricted educational grant from Sepracor.

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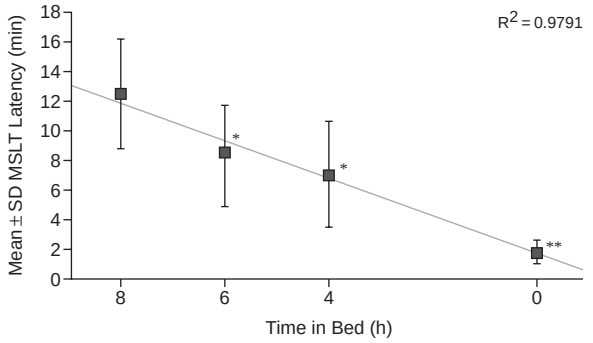
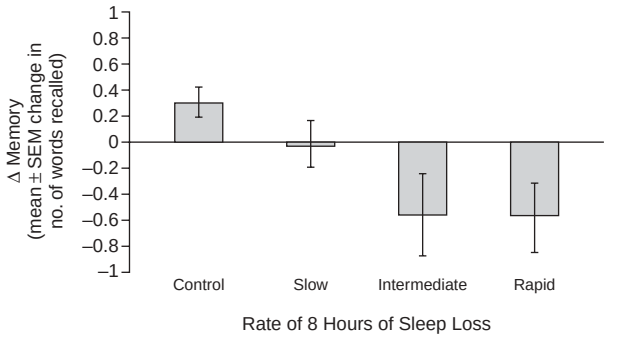
Figure 1. Sleep Latencies on Multiple Sleep Latency Tests (MSLTs) Following 8, 6, 4, and 0 Hours in Bed[a]



[a]Data from Rosenthal et al.[14]
*p < .05 compared with 8 and 0 hours.
**p < .01 compared with all other groups.

Figure 2. Change From Baseline to Last Day of Each Condition in Number of Words Recalled on the Probed Memory Recall Task[a]



[a]Reprinted with permission from Drake et al.[15]

Rosenthal and colleagues[14] determined that increased TST improved alertness. Degree of TST was proportional to alertness. They studied 32 healthy men (ages 20–35 years), who spent 8, 6, 4, or 0 hours in bed. Subjects underwent the same conditions twice, with a period of at least 7 days between sessions. Multiple sleep latency tests (MSLTs) were conducted after the time-in-bed sessions to determine level of alertness (or sleepiness); subjects were instructed to lie in bed for 20 minutes at 2-hour intervals, and electroencephalographic, electromyographic, and electrooculographic recordings were taken. Time to onset of sleep (or sleep latency), which is normally reduced in those who are sleepier, was measured to determine level of alertness of each subject. Subjects who had 0 time in bed had reduced MSLT latencies compared with all the other groups ($p < .01$). MSLTs in the 4- and 6-hour time-in-bed groups were significantly different from those in the other 2 groups ($p < .05$) (Figure 1).

In another study that measured the effects of reduced time in bed and thus reduced TST,[15] 12 healthy men and women, aged 21 to 35 years, were exposed to each of rapid (1 night of 0 hours' sleep), intermediate (2 nights of 4 hours sleep), slow (4 nights of 6 hours' sleep), or no sleep loss over a period of 4 nights, with separations of approximately 1- to 2-week periods. Recall of a word list was significantly impaired by sleep loss ($p < .05$). Rapid accumulation of sleep loss produced a significantly greater decline in memory compared with slow accumulation ($p < .01$) (Figure 2). Another similarly designed study[17] demonstrated that sleep loss reduced pain threshold and increased sensitivity to pain. Finger withdrawal latency to a heat stimulus was reduced significantly by reduced time in bed ($p < .001$).

Reduced TST was also found to reduce glucose tolerance compared with the fully rested condition ($p < .02$) in another time-in-bed restriction study conducted in 11 healthy male volunteers.[18] Evening cortisol concentrations were also elevated ($p = .0001$), as was sympathetic nervous activity ($p < .02$), when TST was decreased. This study demonstrated that reduced TST has a negative impact on endocrine function and carbohydrate metabolism. The authors speculate that, as the effects demonstrated are similar to those seen in normal aging, sleep debt may increase the severity of age-related chronic disorders.[18]

Correlates of Impaired Sleep Continuity

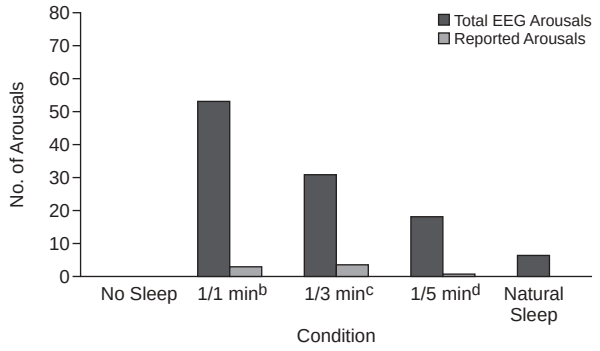
Impaired sleep continuity, which is functionally equivalent to sleep loss, has been associated with impaired alertness,[19] impaired performance and memory,[20,21] and reduced growth hormone[22] and prolactin secretion.[23,24]

Levine et al.[19] randomly assigned 40 healthy subjects (20 men and 20 women; ages 18–35 years) to one of each of the following conditions after a night of sleep deprivation: (1) no sleep, (2) a 100-minute nap with arousals once per minute, (3) a 100-minute nap with arousals every 3 minutes, (4) a 100-minute nap with arousals every 5 minutes, and (5) a 100-minute nap with no arousals. The study was designed to determine the impact of sleep fragmentation, or disturbed sleep continuity, on alertness. Sleep latency tests were conducted at 2-hour intervals thereafter. Figure 3 demonstrates that subjects were predominantly unaware of these episodes of awakenings. Number of arousals (and therefore impaired sleep continuity) was related to reduced sleep latency (and thus increased sleepiness) in the recuperative period (Figure 4).

Bonnet's[20,21] studies, also conducted in healthy young volunteers who were exposed to varying conditions of sleep disruption, demonstrated that impaired sleep continuity results in impaired functioning the next day on performance tasks. It was also determined that as the length of periods of consolidated sleep decreased, performance decrements increased.[21]

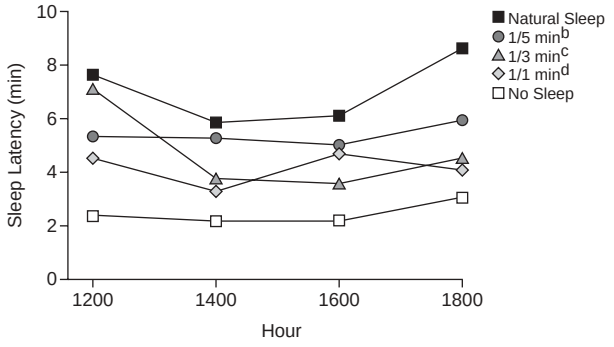
Patients with sleep apnea experience sleep fragmentation related to episodes of apnea.[25] A study conducted in 6

Figure 3. Total Number of Electroencephalogram (EEG) Arousals and Reported Awakenings in Each Representative Nap Condition[a]



[a]Reprinted with permission from Levine et al.[19]
[b]A nap with an arousal every 1 min.
[c]A nap with an arousal every 3 min.
[d]A nap with an arousal every 5 min.

Figure 4. Sleep Latency on Each Sleep Latency Test for Each Recuperative Nap Condition[a]



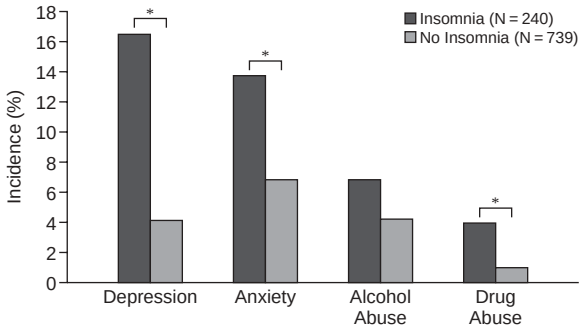
[a]Reprinted with permission from Levine et al.[19]
[b]A nap with an arousal every 5 min.
[c]A nap with an arousal every 3 min.
[d]A nap with an arousal every 1 min.

obese, nondiabetic patients with sleep apnea found that in the absence of nasal continuous positive airway pressure (CPAP) treatment, growth hormone release was reduced. However, when CPAP treatment was instituted, growth hormone levels increased significantly.[22] Growth hormone has lipolytic action, which may be impaired when sleep continuity is disrupted.

CONSEQUENCES OF INSOMNIA

Insomnia has been demonstrated to be associated with increased risk of depression,[26,27] pain in rheumatic diseases,[28] absenteeism,[29–31] and accidents[32] and increased health care utilization.[33] It is believed that these effects are mediated by hyperarousal in insomnia patients.[34]

Figure 5. Insomnia as a Risk Factor for Psychiatric Disorders[a]



[a]Data from Breslau et al.[26]
*95% CI for odds ratio excludes 1.0.

Risk of depression and other psychiatric illnesses associated with insomnia is discussed in more detail elsewhere in this supplement (see Krystal[35] and Benca et al.[36]). Breslau et al.[26] followed 1200 patients, aged 21 to 30 years, from a health maintenance organization. The gender-adjusted relative risk for new onset of major depression during the 3.5-year follow-up period for those with a history of insomnia at baseline was 4.0 (95% CI = 2.2 to 7.0). Risk of anxiety and drug abuse was also increased in individuals with insomnia (Figure 5). The Johns Hopkins Precursors Study followed 1053 men prospectively for a median period of 34 years (range, 1–45 years). Initial data regarding sleep habits during medical school were collected. The relative risk for development of depression was greater in those who reported insomnia during medical school than those who did not (relative risk = 2.0, 95% CI = 1.2 to 3.3).[27]

Risk of absenteeism related to insomnia has been reported in several studies.[29–31] Zammit et al.[29] found that the mean ± SD number of days absent from work per month in their cohort of 261 people with insomnia and 100 controls with no sleep complaint was 1.32 ± 0.15 versus 0.13 ± 0.22 ($p < .0001$). Leger et al.[31] also found that their cohort of 240 insomniacs missed work twice as frequently as 391 "good sleeper" controls. Individuals with sleep problems were more likely than individuals who reported no sleep problems to have missed work in the preceding 4 weeks due to illness (41.4% vs. 29.0%; $p = .003$).[30]

Another study[33] conducted in 373 patients from primary care clinics (aged 18–65 years) demonstrated that mean total health services cost was approximately 60% higher in the insomnia group versus the no insomnia group.

Risk of accidents is also higher in those who experience insomnia. Data from 3 surveys were reported regarding insomnia and agents used to treat insomnia.[32] Prevalence rates for serious accidents or injuries in the preceding year were found to be much higher for chronic untreated insomnia than for normal controls; prevalence rates were 9% versus 2%, a greater than 4-fold increase.[32]

The work of Vgontzas and colleagues[34] indicates that chronic insomnia is pathophysiologically a disorder of hypothalamic-pituitary-adrenal (HPA) system hyperarousal. They demonstrated an overall increase in adrenocorticotropic hormone (ACTH) and cortisol secretion with a normal circadian pattern in their subjects, whereas sleep loss tends to be characterized by unchanged ACTH and cortisol levels or the presence of circadian disturbance. The authors argue that this chronic HPA axis activation may increase risk for psychiatric disorders, such as depression, and also place people with chronic insomnia at risk for a host of medical morbidities associated with this activation, such as hypertension, visceral obesity, and osteoporosis.

INSOMNIA COMORBIDITIES

In addition to the fact that insomnia, whether primary or secondary, has been associated with significant morbidity, it is also well established that insomnia occurs in association with a number of illnesses, both medical and psychiatric.

Epidemiologic studies report prevalence rates of approximately 40% for comorbid psychiatric disorders and insomnia.[37,38] Psychiatric comorbidities include depression and anxiety disorders.[39] Medical comorbidities include illnesses associated with pain and respiratory conditions, among others.[39] Insomnia also occurs with great frequency in perimenopausal women.[40]

Given that these comorbidities are extremely common, and well documented, it is noteworthy that no research has been conducted to date that evaluates treatment of insomnia and its impact on the course, burden, and outcomes of these illnesses. Without such outcomes research, there is no evidence base, nor incentive, for physicians to treat the sleep disturbance in parallel with the primary illness. This area of unmet need in the management of insomnia needs to be addressed in future assessment of hypnotic agents.

CONCLUSIONS AND FUTURE DIRECTIONS

It is thus clear that the basis of our evidence for measuring efficacy of anti-insomnia agents stands at a crossroad. Very few of the measures currently used to determine efficacy have been found to reflect improvement in insomnia-related morbidity. On the other hand, insomnia has been associated with a gamut of adverse outcomes and exists as a comorbid condition with a number of illnesses. Treatment of sleep disturbances should be directed not only at alleviating sleep symptoms, but also at forestalling morbidity, and this goal should be reflected in efficacy measures. In the future, assessments of anti-insomnia agents may look toward improvements in insomnia-related outcomes to determine efficacy. Such therapeutic endpoints may include enhanced alertness, efficacy as augmentation therapy for depression, improvements in pain severity, and decreases in sleep disturbances related to hot flashes.

Drug name: flurazepam (Dalmane and others).

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