PEER REVIEWED | Robyn Woidtke, RN, RPSGT, CCRA, RAC

Eyes Wide Open

A Discussion of Sleep and its Disorders for the Clinical Research Professional

Humans are significantly affected by sleep deprivation, and we spend one-third of our lives asleep; however, unless specified by the sponsor, clinical effects on patients' sleep are often ignored.

The labels for common sleep aids read "may cause insomnia" and "may cause drowsiness"—often simultaneously. How curious that the same drug can impact an individual's ability to fall asleep in opposite ways! Clinical researchers are often the first to obtain knowledge of the properties of innovative medical products. It is part of our job to ascertain a drug's side effects and adverse events, and to discern whether co-morbidities may alter the product's performance. Humans are significantly affected by sleep deprivation, and we spend one-third of our lives asleep; however, unless specified by the sponsor, clinical effects on patients' sleep are often ignored.

More and more information on the interaction between sleep and other physiologic functions, such as hormone secretion, metabolism, and cognitive function, is being uncovered by sleep research. A knowledge of sleep and its disorders helps clinical research professionals to better understand how these interactions occur and to inquire about sleep during their initial and follow-up assessments. What is sleep? What are sleep disorders and their diagnoses? And how can a sleep disorder impact clinical data?

Normal Sleep

Sleep has been described as a temporary state of unconsciousness from which, upon sufficient stimulus, one awakens. Sleep is an extremely complex process, involving changes in neurotransmitters, metabolic rates, and levels of arousal. Not only do these processes differ between wakefulness and sleep, they also vary between various sleep stages.

Sleep has two distinct components, identified by the recording of brain waves via an electroencephalogram (EEG). These are rapid eye movement (REM) sleep, which is the sleep state in which we dream, and the four stages of non-REM sleep (NREM). We experience cycles of REM and NREM throughout the night: our ultradian (less than 24-hour) rhythm.

Individual requirements vary, but most adults require seven or eight hours of sleep per night. Sleep habits also change over the span of one's life: Infants sleep in a polyphasic sleep pattern, in which sleep occurs equally throughout night and day. As the child grows and matures, sleep consolidates and shifts to the nighttime hours. Infants and toddlers have longer sleep periods and an increased percentage of REM sleep compared to adults (see Figure 1).[1]

Figure 1. Hypnogram of Young Adult Sleep

Source: Elsevier Science, 2005.

Physiologic Functioning and Circadian Rhythms

There are many differences between sleeping and waking physiology. Certain functions, such as gastric motility, saliva production, and respiration, slow during sleep. There is increased heart rate variability during REM sleep, and evidence suggests that brain activity also increases during REM. Growth hormone is secreted primarily during slow-wave sleep and thus stimulates its occurrence. Cortisol secretion is directly correlated with the timing of the sleep cycle; levels drop during the night and increase in the morning hours.[2, 4] Many pharmaceuticals can interact or interfere with these systems—circadian rhythms influence absorption, metabolism, and excretion.[5] For instance, certain diseases are affected by the time of the day; arthritis is more painful in the morning, and asthma typically worsens during the night. Thus, the time a drug is administered has important implications for outcomes.[6, 7]

Sleep disorders are problems that interfere with the continuity and quality of sleep. There are more than 80 classified sleep disorders. Typically, the cardinal manifestation of a sleep disorder is daytime or excessive sleepiness, indicative of sleep deprivation. A sleep disorder may affect the function of a drug or device. The sleep disorders described in the next sections are considered the most prevalent, and thus should be considered during the design phase of a clinical trial, especially as part of the enrollment criteria, as the compound may inadvertently impact an undiagnosed sleep disorder (see Figure 3).

A "normal" sleeper falls asleep in stage one, progresses to stage two, and then stages three and four, also known as slow-wave sleep. Each stage is identified by EEG characteristics such as frequency (cycles per second) and amplitude (microvolts). In addition, other parameters such as muscle tone help to distinguish REM from NREM sleep. After approximately 90 minutes of sleep, the first REM period occurs. Slow-wave sleep is more abundant the first third of the night, whereas REM sleep is more prevalent in the last third.

To ascertain the quality of one's sleep, sleep states are plotted over time, from onset of sleep to final awakening, in "sleep architecture" or a hypnogram. This diagram actually shows the cycles and duration of sleep states, and how continuity of sleep cycles may be disrupted by awakenings (see Figure 2). Although researchers still do not understand the exact reason why we sleep, there are many theories. It is commonly accepted that sleep is necessary to memory consolidation and learning. Sleep may aid in body and brain restoration and interruption of neurotransmitters during REM, allowing the receptors time to rest and ensuring appropriate function during wakefulness.[2, 3]
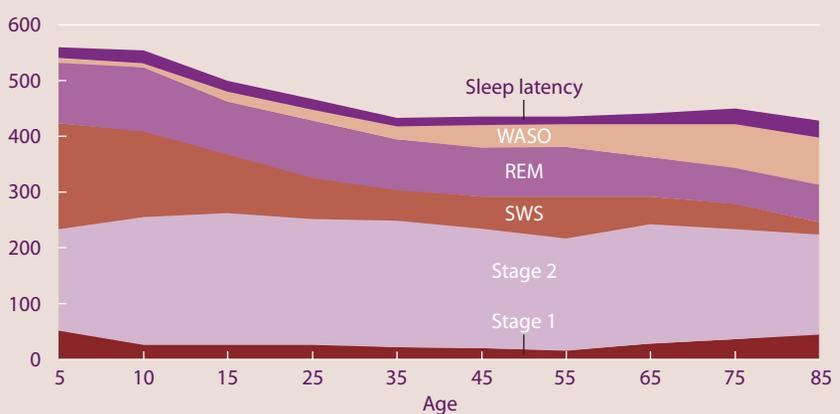
Insomnia

Insomnia is characterized by the inability to fall asleep or stay asleep or by waking up too early. The condition may be transient, intermittent, or chronic. It is more common in postmenopausal women, although men and children may also

Figure 2. Changes in Sleep with Age (One Night)

Sleep latency
WASO
REM
SWS
Stage 2
Stage 1

Age

Source: Elsevier Science, 2005.

present with insomnia. Often, the type of insomnia can be related to external factors, such as chronic illness, painful conditions, transient life-altering stress such as the death of a loved one, divorce, or the birth of a child, or job-related anxieties. It can also be a manifestation of a circadian rhythm disorder, such as advanced or delayed sleep phases, which may be even more difficult to diagnose and treat. Shift work can also disturb the circadian rhythm.

According to the National Institutes of Health (NIH), chronic insomnia is present in 10-30% of the general population.[8] A recent Canadian study found that the prevalence in local populations was 24%.[9] Insomnia can be tricky to diagnose, however, because so many other factors have an impact on sleep,[10] and insomnia may also be a symptom of an underlying cause; thus, asking people if they experience insomnia during a clinical trial may not be enough.

For instance, when asked about insomnia, some subjects may reply that they have trouble falling asleep; when asked why, they may say that their legs feel "creepy crawly" and they have to keep getting up to walk; this suggests that their insomnia may not be insomnia at all, but rather restless legs syndrome (RLS). Directing questions like these can help to define the actual problem. Because the compound being tested may exacerbate an underlying problem,

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Periodic Limb Movements and Restless Legs Syndrome

Periodic limb movements (PLMs) during sleep are common; they can cause arousals from sleep and become more frequent with age. Restless legs syndrome (RLS), however, is actually a neurological problem that occurs during wakefulness; because it influences the ability to fall asleep and maintain sleep, it is classified as a sleep disorder. The last several years have seen an increased awareness of RLS. Its prevalence is approximately 8% and it remains underdiagnosed.[11, 12]

Individuals who have RLS frequently report a "creepy crawly" or "painful" sensation in their legs. The feeling causes them to continually move their legs; they may need to get up and walk, which provides temporary relief, but symptoms return once patients lie down again. RLS can also be associated with uremia and anemia.[13] When inquiring about insomnia, researchers should ask what keeps subjects awake or what wakes them up. They may have RLS but not be aware that what they are feeling has a name and a diagnosis.

Sleep Apnea

Sleep apnea is the cessation of breathing during sleep. Three forms are typically presented: obstructive, central, and mixed. Obstructive sleep apnea (OSA) is caused by the collapse of the upper airway, and corresponds to a lack of breathing control and an absence of ventilatory effort. Central sleep apnea is far less common than OSA, and is often exhibited in heart failure and stroke. OSA may affect some 20 million Americans, the majority of whom are not diagnosed.[14] Gender, obesity, anatomical features such as micro- or retrognathia, and muscular enervation play a role in OSA.[15]

Its major symptom is loud snoring, punctuated with snorts and gasps; snoring indicates turbulent airflow through the upper airway. As the apneic event continues, there is increased respiratory effort to "suck" air through the closed airway, generating large negative intrathoracic pressure as the individual tries to overcome the obstruction. Apneic events are repetitive, occurring as many as 100 times per hour of sleep. Desaturations in blood oxygen levels, surges of sympathetic nervous system activity, and compensatory changes in heart rate (bradycardic or tachycardic arrhythmia) may result, and frequent arousals from sleep are common. Sleep apnea's consequences include hypertension, increased insulin resistance, changes in cognition and vigilance, daytime sleepiness, and erectile dysfunction.[16] Since individuals with OSA may also exhibit nocturia and depression,[17] OSA sufferers exhibit increased healthcare utilization.[18, 19]

Due to the large number of undiagnosed OSA patients, it is highly likely that some research participants will have OSA; this may potentially influence the product. For example, a drug under test for hypertension may not work in the sleep apnea patient, as sleep apnea may be the underlying cause of hypertension.

Risk Assessment and Diagnostic Tests

To determine if there is a problem, ask about an individual's sleep. If anyone has ever told a subject that he or she snores or stops breathing during sleep, the clinical research professional should confirm whether OSA is present. Although not all individuals with OSA are overweight, the majority are. A body mass index greater than 30 and a large neck size (greater than 17 in males and 15 in females) have proven to be accurate predictors of OSA. One should also ask subjects if they are sleepy during the day or fall asleep inadvertently, such as during business meetings or at the movies. A recent German study identified normal sleep latency (the onset to sleep from wake) at 13.9

minutes (+/-6.9 min) in a sample of 100 normal subjects with varying age ranges.[20]

Many questionnaires have been developed to ascertain sleepiness. One of the most widely used is the Epworth Sleepiness Scale (ESS).[21] The ESS is a simple measure, which can be completed quickly within the research environment (see Figure 4).

The quintessential diagnostic test for determining a sleep disorder is the nocturnal polysomnogram, or "sleep study." A polysomnogram is typically conducted in a monitored setting with a full complement of physiologic signals, which include EEG, electrooculogram (EOG, measuring eye movements), electromyogram (EMG, measuring muscle tone), electrocardiogram, and respiratory monitoring including airflow, effort, and pulse oximetry. Other parameters can be added as needed, such as esophageal pH monitoring to test for gastroesophageal reflux. The study is conducted in a laboratory setting over the course of one night.

Other diagnostic tests ascertain how sleepy one is during the day: The multiple sleep latency test (MSLT) measures how quickly someone falls asleep, and the maintenance of wakefulness test (MWT) measures how long one can stay awake.[22] Tests can be conducted in the home setting, but usually these studies collect less data. They are often used to diagnose respiratory disturbances, rather than other sleep disorders.

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Figure 4. Epworth Sleepiness Scale

Score for each activity

0 = no chance of dozing
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

Situation	Chance of Dozing
Sitting and reading	
Watching TV	
Sitting inactive in a public place (e.g., a theater or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in traffic	
Total	

To check your sleepiness score, total the points: if your score is 9 or greater, chances are that the participant would have increased sleepiness.

Conclusion

Labeling is an important component of product commercialization; thus, what research participants report can have a direct impact on labeling. The significance of what is uncovered during a clinical trial cannot be underrated. Research participants' responses to questions regarding sleep in the study of a pharmaceutical product may derive from an undiagnosed sleep disorder, rather than from the product itself.

The field of sleep medicine is growing. More and more clinical data are being gathered as new information emerges about sleep, the circadian system, and the interaction between sleep and other conditions. OSA, for example, has been found to contribute to insulin resistance, hypertension, and depression.[23-25] We must consider the psychological impact of poor sleep not just on quality of life, but on diagnostic measures commonly used in the research process.

Clinical research professionals make a significant difference in the medical product development process. We are the "senses" of the medical product industry. For those who draft protocols, the fact that we sleep approximately one-third of our lives, awareness of the complexities of sleep, and a few simple questions may have a significant impact on study results, and ultimately on the commercialization of a medical product.

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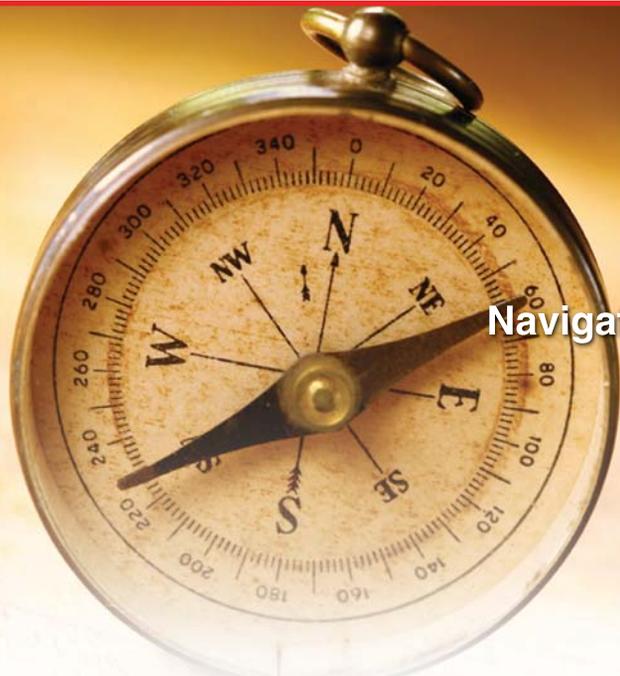
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