Sleep Disturbance and HIV Disease
Andres Sciolla, MD

When people are asleep, we usually describe them as having their eyes closed, not moving, unresponsive to the environment. Although accurate in many ways, this description reflects a conception of sleep as a "passive" behavior. In actuality, sleep is much more complex.

Part of that complexity stems from the reciprocal interactions between the sleep-wake cycle and other physiological processes, such as hormonal production and immune function. Another aspect is the myriad of medical and psychosocial problems that people with HIV disease face that may also interfere with sleep, making it easy to overlook, under-diagnose, and undertreat HIV-associated sleep disturbance. Sleep disorders may arise due to a psychiatric disorder, a medical condition, the effects of a substance (a drug of abuse or a medication), pain, frequent urination or diarrhea, or an abnormality in sleep-wake generating or timing mechanisms. In a substantial proportion of individuals who complain of sleep disturbance, there is no apparent cause other than HIV disease. (See "Sleep Disturbance in Early HIV Infection," page 5, for more on the causes of insomnia.)

The identification of the cause of the disturbance is the cornerstone of effective therapy. Treatment is crucial not only because of the physical affects of sleep disturbance, but also because of its impact on quality of life, work, daily functioning, and cognitive performance.

Sleep Patterns and Function

Despite this complexity, there are fundamental characteristics of sleep that are clear and well-established. One is that periodic sleep is necessary; the other is that sleep has a rhythm that is relatively independent of external conditions. If a person is completely isolated from environmental changes of light, temperature, social cues, and the knowledge of time, his or her sleep-wake cycle will gradually drift from a strict 24-hour cycle and start approximately every 25 hours. This near 25-hour physiological day corresponds to the frequency of the circadian (Latin for "about one day") pacemaker located in the brain's hypothalamus.

This circadian cycle varies with age. Newborns have no discernible sleep-wake pattern. Young children have a biphasic pattern, with an afternoon nap in addition to the main nighttime sleep episode. Adults living in temperate climates normally have only one main sleep episode. In the healthy elderly, daytime napping becomes more common and nighttime sleep more interrupted.

In addition to the circadian sleep-wake rhythmicity, there are two main types of sleep: slow wave sleep (SWS), which consists of four stages; and rapid-eye-movement (REM) sleep. When a person falls asleep, electroencephalogram (EEG) waves show progressively slower frequencies and higher voltages, corresponding to the successively deeper stages of SWS, labeled 1 through 4. In stage 4, sleep is deepest. After a period of 30 minutes to 45 minutes, the sleeper retraces the same stages in reverse order.

About 90 minutes after the onset of sleep, the EEG abruptly changes, showing high frequency, low voltage activity similar, but not identical, to the waking state. During this REM stage, however, the person remains asleep and immobile. The only muscles that are active are those controlling respiration, the middle ear ossicles, and the movements of the eyes. Between 74 percent and 95 percent of sleepers recall dreaming when awakened from REM.
Can there be anything as sweet as a good night’s sleep, anything as frustrating and debilitating as a night of tossing and turning? In the world of nighttime activities, sex gets all the attention, but most of us would trade passion for slumber if forced to make a choice.

Sleep disturbance is a common symptom of many psychological disorders and serious illnesses. HIV disease—with components of emotional and physical distress—is fertile ground for insomnia, hypersomnia, and fatigue. The articles in this issue of FOCUS address HIV-related sleep disturbance, defining what is known about this complex disorder and the comparatively simple approaches to alleviating it.

Andres Sciolla’s article provides an accessible overview of the function and structure of sleep and ways to regain control over sleep patterns. Perhaps the most compelling information in this article is that there are aspects of sleep that are learned and interventions that can reteach our minds and bodies these essential patterns. By reclaiming sleep as repose and isolating it from the stuff of life, the bedroom becomes a haven; by observing sleep hygiene guidelines, sleep becomes an attainable goal rather than some mysterious gift. There are no panaceas here and some of us will still be counting sheep, but there are practical approaches that will help the majority of those with sleep disturbances.

At the same time, there are factors specific to serious illness and unique to HIV disease that make sleep difficult. As disease progresses, factors like pain, unfortunate interaction among medications, breathing difficulties, and frequent urination can all interrupt sleep and may be able to be only partially mitigated. More arcane HIV-related processes like the interactions of peptides described by Jeannine White, Merrill Mitler, and Denis Darko in their FOCUS article may make sleep difficult and, at least for now, are untreatable.

Sleep is crucial for healing and for feeling well. To the extent that providers help clients manage symptoms ranging from pain to depression, they should consider practical responses, including education, to sleep disorders.
sleep, or a feeling of nonrestorative sleep; 2) Hypersomnia type (excessively long nocturnal sleep or excessive sleepiness during waking hours); 3) Parasonmia type (abnormal behaviors occurring in association with sleep or sleep transitions); and 4) Mixed type.

The most common clinical picture resembles the pattern of sleep for older people: as people age, they complain of difficulty maintaining rather than initiating sleep, and of the need to take daytime naps. Typically, HIV-infected people report frequent awakenings during the night, some lasting an hour or more. Sometimes this is accompanied by early awakening and the inability to fall back asleep. Not feeling refreshed upon awakening or daytime napping are common and sometimes can be the sole symptom of sleep disturbance.

A careful history helps clinicians rule out other potentially treatable causes of sleep disturbance, such as primary sleep disorders, medical or neurological conditions, and mood, anxiety, and substance-related disorders. For example, both HIV-associated and depression-associated sleep disturbance can occur successively and simultaneously in the same person, and these disturbances may be indistinguishable from each other. Diagnosis in such cases is aided by the fact that sleep disturbance, by definition, cannot be the sole symptom of depression, and if it is the sole symptom, then the disturbance is likely to be HIV-related. These guidelines also apply to HIV-related fatigue.

While there are no published reports about the course of HIV-related sleep disturbance, clinical experience and research indicate that symptoms may remit or recur spontaneously after a few weeks or months, with no apparent relation to other events. Overall, both the prevalence and the severity of symptoms increase in the later stages of HIV disease. Some later stage patients may have a sleep-wake pattern with no discernible rhythmicity, and may move, seemingly at random, between short episodes of wake and sleep. It is currently unclear to what extent this worsening may be the result of HIV disease progression or the increased prevalence of confounding factors, such as use of medications, opportunistic infections, delirium, or dementia.

**Treatment**

Currently, the pathogenic mechanism of HIV-associated sleep disturbance remains obscure. Consequently, there are no therapies available that attempt to correct the specific dysfunction underlying the disturbance. While there have been no published controlled trials regarding the effects of standard sleep interventions on HIV-associated sleep disturbance, anecdotal reports suggest that pharmacological agents and behavioral techniques offer significant, albeit partial, relief. Clinicians working with clients with HIV-related sleep disturbance should consider the following guidelines.

First, pharmacological agents generally offer only partial relief and add to the burden of complicated pharmacological regimens already endured by many seropositive people. Therefore, it seems wisest to start with a trial of behavioral techniques before administering sleep medications.

Second, the standard behavioral techniques used in the treatment of insomnia are relaxation training, habit training, and reversal of negative conditioning. The exact combination of techniques must be tailored to each individual patient. Fundamentally, all relaxation techniques involve a quieting of ruminative thoughts, replacing them with a repetitive, simple mental activity such as counting breaths or spiritual mantras, relaxation of the muscles, slowing of heart rate and respiration, and a decrease in the activity of the sympathetic nervous system (the system that prepares an organism to cope with stress). Little evidence suggests one relaxation technique over the others. Experts believe that the provider’s enthusiasm and encouragement to the client to practice regularly are probably more important than the specific technique.

Habit training involves helping the client relinquish certain habits that may have been spontaneously adopted to counteract insomnia or daytime sleepiness, but which stand in the way of physiological correction of the problem. These may include sleeping late, taking naps during the day, and excessive use of caffeinated beverages especially late in the day. Adhering to regular wake-up times and eliminating naps avoids further disruption of the circadian sleep-wake cycle. Eliminating caffeine in the evening (caffeine has a half-life of four to five hours) decreases arousal and stimulation of the brain. A light lunch with no alcoholic beverages and remaining physically active

Because behavioral responses to sleep disturbance can offer significant relief, it seems wisest to try them before using sleep medications.
in the afternoon may reduce afternoon naps. Heavy exercise early in the evening is associated with more restorative and less interrupted nighttime sleep, while exercise late in the evening is associated with poorer sleep quality.

Reversal of negative conditioning is based on the fact that some behaviors or physiological responses can be triggered by the repetition of specific stimuli. After a period of time, individuals with insomnia may associate going to bed with expected discomfort. If a person experiences improved sleep outside the usual bedroom or away from home, negative conditioning might be at play. The fear of difficulty sleeping, which increases arousal, contributes to sleep disturbance itself. In such cases, individuals should not go to bed until they feel sleepy. After 20 to 30 minutes of failing to fall asleep, they should also get up from bed and resume normal activities until sleepy. The rationale for this approach is to associate being in bed with relaxation and sleep. Along the same line, in bed, clients should avoid pursuing activities that increase arousal such as snacking, watching television mysteries, or reading adventures.

If behavioral approaches are unsuccessful, clinicians should consider pharmacological interventions. These include longer-acting and shorter-acting benzodiazepines, antihistamines, and sedating antidepressants. Benzodiazepines bring on muscle relaxation, sedation, and sleep induction, and may lead to tolerance, physical dependence, and withdrawal syndromes. Half-lives vary greatly among the different agents, with some as short as three hours (triazolam) and others as long as 48 hours (clordiazepoxide). The shorter-acting benzodiazepines have the advantage of lessened “hangover” upon waking. However, they may produce more rapid and intense withdrawal symptoms, raising the risk of habituation, daytime withdrawal, agitation, or anxiety.

In seropositive as well as elderly clients, longer-acting compounds may accumulate in the body over days or weeks and lead to insidious oversedation, personality change, or mental deterioration. Clinicians have long observed that many seropositive people behave pharmacologically like the elderly: they require less than the habitual dose of medications to reach the desired effects and are prone to experience side effects or toxicity. Unlike barbiturates and benzodiazepines, antihistamines (such as diphenhydramine) and sedating antidepressants (for example, doxepin and trazodone) do not produce physical dependence, although they do have a variety of side effects that may be difficult to tolerate.

There are no reports in the literature of experimental therapies for HIV-associated sleep disturbance. However, researchers are studying the effects of artificial light, and anecdotal reports suggest that melatonin (sold at health food stores) may respond to insomnia.

**Conclusion**

Sleep disturbance can be treated, and appropriate treatment, particularly in the case of sleep disturbance secondary to anxiety or depression, can be very effective. While pharmacological treatment may have side effects that are sometimes poorly tolerated by those with diminished health or neurocognitive impairment, behavioral therapy can be effective.

**Clearinghouse: HIV and Sleep**

**References**


Sleep Disturbance in Early HIV Infection

Jeannine L. White, PhD, Merrill M. Mitler, PhD, and Denis F. Darko, MD

Immune proteins may have a role in HIV-related sleep disturbance: they promote slow wave sleep in animals and induce fatigue when used to treat cancer.

References


National Sleep Foundation, 1367 Connecticut Avenue NW, Washington, DC 20036. Provides printed materials about common sleep disorders and referrals to accredited sleep disorder centers around the country.

Andres Sciolla, MD, HIV Neurobehavioral Research Center (HNRC), University of California, San Diego, 2760 Fifth Avenue, Second Floor, San Diego, CA 92103, (619) 543-5065.

Wilford Hall Sleep Disorder Center, 59 MDW 4/WHMC, 2200 Bergquist Drive Suite 1, Lackland AFB, Texas 78236-5300, (210) 670-7621.

See also references cited in articles in this issue.
sleep quality, and excessive daytime sleepiness. However, more recent studies using objective and subjective measures of sleep found no significant influence of ZDV on nocturnal sleep or daytime alertness.

Finally, objective measures of nocturnal sleep, daytime sleepiness, and cognitive-motor performance suggest a complex relationship between HIV disease progression, HIV infection of the central nervous system, and sleep, and the neuropsychological deficits that arise in early HIV infection may be related to sleep disturbance and daytime fatigue. This is particularly important because HIV can be found in the central nervous system even in the early stages of infection, and it has been estimated that up to 50 percent of people with AIDS develop at least a mild neurocognitive disorder.

The Role of Immune Proteins

Having excluded psychiatric, psychological, medical, and pharmacological variables in early stage sleep disturbance, researchers have begun to examine the effect of HIV infection on the brain itself. Evidence continues to accumulate to support a role for the immune proteins "tumor necrosis factor alpha" (TNF-α) and "interleukin-1 beta" (IL-1 β) in the sleep changes and fatigue commonly seen in HIV infection. These peptides are produced by immune system cells known as monocytes or macrophages and have been shown to promote slow wave sleep in animals and fatigue when used to treat cancer. These peptides may even have a role in the regulation of normal sleep physiology. Since HIV infection is concentrated in cells of the immune system, the possibility of derangement in the normal ebb and flow of these peptides may explain the consequent disruption of sleep and daytime readiness to think and work; in fact, levels of TNF-α and IL-1 β are elevated in the blood of people with HIV infection.

While the function of slow wave sleep (also known as stages 3 and 4 of non-rapid eye movement [NREM] sleep) is not completely understood, its distribution within the nighttime sleep period has been well-studied. Among healthy adults, slow wave sleep is distributed primarily during the first portion of the night and decreases rapidly in intensity and duration as the night progresses. Sleep, particularly slow wave sleep, is thought to be involved in tissue restoration after extended periods of wakefulness. Studies in healthy individuals have shown an increase in immune activity that was significantly related to the onset of slow wave sleep.

Increased slow wave sleep in the latter portions of the night is a consistent feature of early HIV infection. The specificity, novelty, and subtlety of this feature is noteworthy. Similar results have been found in slow wave sleep in the latter portion of the principal sleep period of infected cats who were permitted only one eight-hour sleep period per day. Thus, in at least two species, this abnormal sleep structure accompanies initial changes in immune function after immunodeficiency virus infection. These distortions of the normal temporal distribution of slow wave sleep appear to provide physiological markers for the early effects of HIV disease.

Conclusion

Sleep structure distortion is one of the earliest and most consistent physiological signs of HIV infection. While the reasons for this distortion remain obscure, new data suggests that abnormal levels of peptides such as TNF-α might somehow be involved. It is possible that the observed abnormalities in sleep structure and increases in peptide levels are also related to the pervasive fatigue that so often disables seropositive individuals. Upcoming clinical trials will evaluate medications for efficacy in treating HIV-related fatigue and sleep disturbance. The first medications tested were chosen for their ability to decrease levels of TNF-α, and this could lead to therapies that would restore sleep and improve quality of life.

New Book on Dementia

In the tradition of FOCUS, AHP presents the UCSF AIDS Health Project Monograph Series, offering brief, accessible, and practical responses to challenging issues. We have just published the first volume in the series: AIDS and the Impact of Cognitive Impairment, a 96-page handbook that describes the range of conditions that cause cognitive impairment and the approaches providers can take in response to them. It is available from AHP for $7.95 (plus shipping and handling) by calling (415) 476-6430.
Recent Reports

Behavioral Intervention for Insomnia

A study of a cross-section of insomnia sufferers found that cognitive-behavioral therapy led to a dramatic reduction in sleep disturbance and cut dependency upon sleep medication by more than 50 percent.

The study sample consisted of 64 women and 36 men, with an average age of 45 years. Diagnoses of insomnia varied, including insomnia associated with psychopathology, affective and anxiety disorders, and drug-dependency. Of the group, 84 percent had reported some use of sleep medications in the past month.

Weekly therapy sessions were provided on an individual basis, and gradually incorporated behavioral, cognitive, educational, and medication-withdrawal components. Behavioral intervention included restricting the time spent sleeping, regulating the sleep-wake schedule, curtailing sleep-incompatible activities, and minimizing time spent awake in bed. Cognitive therapy addressed the common fears about insomnia and misconceptions about sleep disturbances. Sleep-hygiene education focused on the effects of chemical and physical factors—like alcohol and exercise—on sleep patterns.

Although total sleep time increased only marginally following treatment, other measures of insomnia improved significantly for the entire sample. The total time spent awake in bed decreased by 45 percent, difficulty falling asleep decreased by 42 percent, wake after sleep onset decreased by 42 percent, and early morning awakening decreased by 50 percent. Notably, the number of sleep-medication users dropped by 54 percent, suggesting that psychological treatment can be as effective as the more accepted pharmacotheraphy.

Sleep Disturbances and HIV

A study comparing 45 HIV-infected individuals with a control group, matched for age and gender, found more severe self-reported sleep disturbances in the seropositive population.

Using the Wheatley Stress Profile (high score of 10), the two groups were measured for severity of five insomnia-related factors. Overall, HIV-infected subjects reported greater disturbance with sleep onset, early morning awakening, nocturnal awakening, and well-being upon waking.

There were no statistically significant correlating factors for sleep disturbance in the control group. Although the mean insomnia score did increase progressively in relation to the severity of stress in daily life, the link between stress and insomnia severity in control subjects was not as significant as the link between HIV infection and insomnia. The mean insomnia score of control subjects with stress was 2.5 while their matched HIV-infected subjects had a mean score of 3.5. Neither gender nor age was correlated to insomnia severity for either group; formal AIDS status was not correlated to insomnia in the HIV-infected group.

HIV-Related Alterations in Sleep Physiology


Alterations in sleep architecture accompany HIV infection, but are not correlated to HIV-related opportunistic conditions or psychological responses. Two small studies found that the sleep cycles of asymptomatic seropositive men differed from normative patterns.

Subjects from both studies were screened for chemical use and a present or past psychiatric history. Physiological testing evaluated sleep efficiency—total sleep time divided by time in bed—and the pattern of sleep cycles, including “slow wave sleep,” “rapid eye movement”
Fatigue and HIV Progression


Medical variables associated with HIV progression predicted fatigue and its disabling effects on daily activities and employment, according to a small study of subjective fatigue. It remains unclear, however, whether fatigue is the result or the cause of HIV progression.

Fourteen men with symptomatic HIV disease, 44 asymptomatic seropositive men, and 50 seronegative men responded to a questionnaire regarding subjective fatigue. Over half of the symptomatic men reported that fatigue was “often or always” a problem in contrast to 11 percent of the asymptomatic group and 10 percent of the seronegative group. HIV infection also correlated with early awakening and use of sleep medications. None of the seronegative group reported that fatigue interfered with daily activities, while 9 percent of the asymptomatic group and 50 percent of the symptomatic group said they experienced daily interruptions of fatigue.

A small study of subjects at various stages of infection found that while HIV progression appears to influence sleep quality, there is no evidence that zidovudine (ZDV) therapy has any effect on it.

A group of 47 men and three women were classified by stages of HIV progression. Of the 30 people who were classified in the final stages of HIV disease by Centers for Disease Control and Prevention (CDC) standards, 19 were undergoing ZDV therapy.

Patients in the final stages of HIV disease reported significantly higher levels of sleep disturbance than did patients in earlier stages. Specifically, they reported reduced quality of sleep, difficulty falling asleep, and frequent need of sleep medications. Although progression was clearly linked to sleep disturbance, the study could not rule out the effects of possible contributing factors, such as depression.

Contradicting earlier studies, ZDV treatment did not significantly affect sleep quality. The researchers theorized that this result may reflect the current trend of prescribing lower daily doses than had been the standard in earlier years of treatment.

(REM) sleep, and non-REM (NREM) sleep.

The first study sample (AIDS, 1990) was comprised of 10 asymptomatic HIV-infected men. Although sleep efficiency was above 90 percent, there was an increase in slow wave sleep in the second half of the night—different from established normative sleep patterns. The second study involving 14 seropositive and 10 seronegative men found specific alterations in the pattern of slow wave sleep, REM, and NREM sleep cycles, as well as total percentage of slow wave sleep time throughout the night.

Reported sleep complaints for both groups were vague and mild in severity, mostly relating to problems falling asleep and difficulties remaining asleep.

Surprisingly, there was no correlation between these reported sleep disturbances and the observed alterations in sleep cycles. However, these studies did confirm that sleep disturbances occur both before and independently from HIV-related secondary infections or psychiatric factors.

Zidovudine and Sleep


A small study of subjects at various stages of infection found that while HIV progression appears to influence sleep quality, there is no evidence that zidovudine (ZDV) therapy has any effect on it.

A group of 47 men and three women were classified by stages of HIV progression. Of the 30 people who were classified in the final stages of HIV disease by Centers for Disease Control and Prevention (CDC) standards, 19 were undergoing ZDV therapy.

Patients in the final stages of HIV disease reported significantly higher levels of sleep disturbance than did patients in earlier stages. Specifically, they reported reduced quality of sleep, difficulty falling asleep, and frequent need of sleep medications. Although progression was clearly linked to sleep disturbance, the study could not rule out the effects of possible contributing factors, such as depression.

Contradicting earlier studies, ZDV treatment did not significantly affect sleep quality. The researchers theorized that this result may reflect the current trend of prescribing lower daily doses than had been the standard in earlier years of treatment.
DID YOU KNOW?

You can access a FREE searchable archive of back issues of this publication online! Visit http://www.ucsf-ahp.org/HTML2/archivesearch.html.

You can also receive this and other AHP journals FREE, at the moment of publication, by becoming an e-subscriber. Visit http://ucsf-ahp.org/epubs_registration.php for more information and to register!

ABOUT UCSF AIDS HEALTH PROJECT PUBLICATIONS

The AIDS Health Project produces periodicals and books that blend research and practice to help front-line mental health and health care providers deliver the highest quality HIV-related counseling and mental health care. For more information about this program, visit http://ucsf-ahp.org/HTML2/services_providers_publications.html.