



January 1999

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### Recommended Citation

Phillips, K. D. (1999). Physiological and pharmacological factors of insomnia in HIV disease. *Journal of the Association of Nurses in AIDS Care*, 10(5), 93-97.

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# *Physiological and Pharmacological Factors of Insomnia in HIV Disease*

Kenneth D. Phillips, PhD, RN

For almost two decades, HIV infection has been a progressive disease leading to early morbidity and mortality for more than a million Americans (Centers for Disease Control and Prevention [CDC], 1998). Although HIV infection strikes people of any age, it continues to be a disease of young persons in relatively good health. Persons with HIV (PWHIV) who are in the advanced stages of the disease typically experience very troubling symptoms. Insomnia is one of these bothersome symptoms.

Recent advances in diagnosis and treatment of HIV disease have resulted in a declining AIDS death rate (Emeni, 1996). The declining death rate is followed by a substantial increase in the prevalence of AIDS. As of June 1998, there were 352,379 men, women, and children living with HIV disease (CDC, 1998). With more people living longer and doing better in the face of HIV infection, management of symptoms such as insomnia will be of even greater importance.

Insomnia refers to unsatisfactory duration, efficiency, or quality of sleep that is experienced 3 or more nights per week (Morin, 1993). Luce and Segal (1969) classified insomnia into the following three types: problems with falling asleep, problems with staying asleep, and problems with early awakening.

Sleep disturbance is a frequent symptom of HIV infection (Cohen, Ferrans, Vizgirda, Kunkle, & Cloninger, 1996) that contributes to fatigue, disability, eventual unemployment (Darko, Mitler, & Henriksen, 1995), and a decreased quality of life. Many symptoms of HIV disease often lead to insomnia (Flaskerud & Ungvarski, 1995). Organic brain diseases (Wiegand, Moller, Schreiber, Krieg, & Holsboer, 1991), psychological factors (Norman, Chediak, Kiel, & Cohn, 1990), substance dependency (Flaskerud &

Ungvarski, 1995), and the side effects of many antiretroviral therapies and other drugs (Chohan, 1999) used to treat HIV disease may produce insomnia. Although helping the client manage sleep disturbance is of great importance, available information in this area remains modest.

Insomnia frequently begins prior to the diagnosis of HIV, and it continues throughout the disease (Norman, 1990). In fact, daytime sleepiness may be a presenting symptom of HIV disease (Norman et al., 1992). PWHIV are more likely to be unemployed, feel fatigued throughout the day, sleep more, nap more, and have diminished alertness (Darko, McCutchan, Kripke, Gillin, & Golshan, 1992). Fatigue and insomnia have been found to contribute to mortality in PWHIV (Darko et al., 1992). During polysomnography, sleep architecture changes have been noted in PWHIV in that deeper sleep (Stages III and IV) is more prevalent in the last half of the sleep period (Norman, 1990). Wiegand and colleagues (1991) reported longer sleep onset latency, reduced total sleep time, reduced sleep efficiency, and more time spent awake in PWHIV. Ferini-Strambi and colleagues (1995) reported significant reductions in deeper sleep in PWHIV.

## **Physiological Factors Related to Insomnia in HIV Disease**

Neurotransmitters, opiate peptides, hormones, and cytokines are important in regulating sleep. Issues related to sleep and these physiological factors in HIV disease will be presented. These endogenous substances are listed in Table 1.

Many changes occur in the hypothalamic-pituitary-adrenal axis (HPAA) in HIV infection. Central to these

**Table 1. Endogenous Substances Important in the Regulation of Sleep**

Neurotransmitters	Serotonin
	Norepinephrine
	Epinephrine
	Acetylcholine
	Histamine
	Adenosine
	Gamma-amino-butyric acid (GABA)
Opiate peptides	Endorphins
	Enkephlins
Hormones	Corticotropin Releasing Factor
	Growth Hormone Releasing Factor
	Growth Hormone
	Adrenocorticotropin Hormone
Cytokines	Cortisol
	Interleukin-1
	Interleukin-6
	Tumor necrosis factor

changes is the fact that the circadian rhythm of the HPAA is lost in PWHIV (Rondanelli et al., 1997).

Growth hormone (GH) is important in the regulation of sleep. GH decreases in PWHIV. GH secretion increases slow-wave sleep (SWS) and decreases the number of awakenings (Astrom, Christensen, Gjerris, & Trojaborg, 1991; Astrom & Lindholm, 1990). GH administration may be useful to treat the wasting syndrome in PWHIV (Hellerstein, Kohn, Mudie, & Viteri, 1990; Jenkins & Ross, 1999). The effects of GH administration on sleep in PWHIV need to be tested.

Corticotropin-releasing factor (CRF) secretion increases in HIV disease (Azar & Melby, 1993). It has been suggested that interleukin-1- $\beta$  (IL-1- $\beta$ ) may be responsible for the increase in CRF (Sapolsky, Rivier, Yamamoto, Plotsky, & Vale, 1987). Increased secretion of CRF is associated with lighter sleep, decreased time in SWS, and increased time spent in Stage I and Stage II sleep (Holsboer, von Bardeleben, & Steiger, 1988).

In turn, CRF stimulates the production of adrenocorticotropin hormone (ACTH). Increased secretion of ACTH reduces rapid eye movement (REM) sleep and reduces total sleep time (Born, Spath-Schwalbe, Schwakenhofer, Kern, & Fehm, 1989).

ACTH stimulates the secretion of cortisol. Profound hypocortisolemia is characteristic in the early

stages of HIV disease, but hypocortisolemia is observed in the later stages of the disease. HIV replication is enhanced by cortisol (Markham, Salahuddin, Veren, Orndorff, & Gallo, 1986). Hypercortisolemia is related to increased wakefulness, lighter sleep, and reduced REM sleep (Born et al., 1986).

Three cytokines have been shown to produce sleep. These cytokines, IL-1- $\beta$ , interleukin-6 (IL-6), and tumor-necrosis factor alpha (TNF- $\alpha$ ), are markers of immune activation. These cytokines are elevated in the blood of PWHIV, and they are associated with an increase in HIV replication and the progression of the disease.

IL-1- $\beta$  stimulates the production of CRF and may contribute to the hypocortisolemia that is seen in HIV disease (Azar & Melby, 1993). IL-1- $\beta$  increases total sleep time and non-REM (NREM), and decreases REM and SWS (Borbely & Tobler, 1989). However, in HIV disease, increased secretion of IL-1- $\beta$  may lead to insomnia because of its effects on CRF.

IL-6 stimulates the production of ACTH and cortisol concentrations. IL-6 decreases SWS in the first half of the sleep period, but it increases SWS in the second half (Spath-Schwalbe et al., 1998).

TNF- $\alpha$  increases NREM sleep, decreases REM sleep (Graf, Heller, Sakaguchi, & Krishna, 1987), increases SWS (Kapas & Krueger, 1996), and increases total sleep time (Graf et al., 1987). In PWHIV, TNF- $\alpha$  elevates to as much as six times the normal level. Significant relationships are seen between TNF- $\alpha$  and delta-wave sleep in HIV infection; increased delta-wave sleep and sleep fragmentation are seen early in the infection and decreased delta-wave sleep appear in advanced HIV disease (Darko, Miller, et al., 1995). This raises the question that IL-6 may indirectly lead to insomnia through the HPAA.

It is impossible for the clinician to address these diverse physiological alterations in the immune and endocrine systems. Being aware of these changes and intervening when possible is essential. For instance, vigilant monitoring and treatment for concurrent infections may decrease the level of immune system activation and viral replication. In that regard, it is important to remember the importance of monitoring

disease progression, optimizing antiretroviral therapy, and assisting the client to adhere to treatment regimens, all of which are important aspects in the treatment of insomnia.

### Symptoms Related to Insomnia in HIV Disease

Sleep promotion requires adequate control of other HIV-related symptoms. Anxiety and depression are related to sleep quality. Symptoms produced as a result of opportunistic infection and opportunistic malignancy (i.e., pain, abdominal cramping, diarrhea, incontinence, itching, burning, fever, night sweats, cough, and dyspnea) contribute to the sleeplessness experienced by PWHIV (Lashley, 1999).

Restoring restful sleep depends on effective management of other HIV-related symptoms. This may be where clinicians can be most effective in restoring and promoting sleep. As an example, managing the anxiety and depression that often accompany HIV infection and insomnia are very beneficial to promoting sleep. Benzodiazepines are useful in treating anxiety, but they must be used with great caution for patients who are concurrently taking protease inhibitors. Short-acting benzodiazepines are sometimes prescribed for individuals who have trouble falling asleep. Intermediate-acting benzodiazepines are employed when the person has trouble staying asleep. Long-acting benzodiazepines may be useful for those who are experiencing significant anxiety in addition to the insomnia. Sedating antidepressants such as nortriptyline, buspirone, or trazadone may help with the insomnia (Weilburg, 1995). Likewise, management of other related symptoms is just as essential when planning and implementing interventions to promote sleep.

### Pharmacological Factors Related to Insomnia in HIV Disease

Many of the drugs used to treat HIV infection and its complications have insomnia as a side effect. A number of the nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and the drugs used to treat opportunistic malignancies significantly impact sleep.

**Table 2. Medications and Sleep in HIV Disease**

Organisms targeted	Drug	Effect on sleep
HIV	Didanosine (ddI)	Insomnia
	Lamivudine (3TC)	Insomnia
		Sleep disorders
	Stavudine (d4T)	Insomnia
	Zalcitabine (ddC)	Insomnia
	Zidovudine (AZT, ZDV)	Insomnia
		Somnolence
	Delavirdine	Insomnia
	Nevirapine	None reported
	Indinavir	Insomnia
		Somnolence
	Nelvinavir mesylate	Insomnia
		Sleep disorders
		Somnolence
		Insomnia
	Somnolence	
Viruses	Saquinavir	None reported
	Acyclovir	None reported
	Foscarnet	Insomnia
Pneumocystis carinii		Somnolence
	Ganciclovir	Somnolence
	Atovaquone	Insomnia
	Clindamycin	None reported
	Dapsone	Insomnia
	Pentamidine	None reported
	Primaquine	None reported
	Trimethoprim-sulfamethoxazole	None reported
Trimetrexate	None reported	
Mycobacterium tuberculosis	Ethambutol	None reported
	Isonizid	None reported
	Pyrazinamide	None reported
	Rifampin	Drowsiness
Mycobacterium avium		Somnolence
	Azithromycin	Insomnia
	Ciprofloxacin	Somnolence
		Somnolence
	Clarithromycin	None reported
	Clofazimine	None reported
	Ofloxacin	Insomnia
Fungi		Sleep disorders
	Rifabutin	None reported
	Amphotericin B	None reported
	Fluconazole	None reported
	Flucytosine	Sedation
	Itraconazole	Somnolence
	Ketoconazole	Somnolence

SOURCE: Adapted from Chohan (1999).

These drugs are presented in Table 2. Reduction of viral load results in less immune and endocrine

activation that may lead to better quality of sleep. There are no other alternatives for many of these drugs; however, altering administration times may be beneficial in promoting sleep. In cases where there is another suitable drug that is less of a detriment to sleep, that drug might be considered.

Other factors related to insomnia include the use of sedatives (i.e., alcohol, benzodiazepines, barbiturates, and narcotics) and the use of stimulants (i.e., coffee, tea, cola, and chocolate). Many over-the-counter medications and alternative therapies may produce insomnia. Assessment of these factors may help the clinician to identify factors that may be disrupting sleep. Once such factors have been identified, the clinician will be able to counsel the patient regarding their effects on sleep.

Insomnia is a serious problem for the PWHIV in that, for many individuals, it is severe enough to drastically diminish the quality of life that they experience. Nursing's holistic perspective of patient care places nurse clinicians in a unique position to address the symptoms of HIV disease. Insomnia is a prime example in which a holistic approach is needed, for it is impossible to improve sleep quality without addressing the many other symptoms that are experienced by PWHIV. A careful history of the patient who is sleeping poorly may identify physiological, psychological, and environmental factors that will allow nurses to effectively intervene and improve sleep quality. Combining western pharmacological therapies and complementary therapies may optimize rest for these sleepless individuals. What the PWHIV needs is problem-solving care based on careful assessment and sound scientific data. Not only are these factors important to clinicians and the care that they provide, but these factors provide many research questions that remain unanswered. Clinicians and researchers have the opportunity to work collaboratively to find and validate effective interventions that can promote sleep and decrease the adverse effects of insomnia for patients with HIV/AIDS.

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