

HIV-RELATED SLEEP DISORDERS

- **Sleep Disorders** occur in a bout 30-40% of HIV+ individuals. Insomnia is a subjective complaint of insufficient, inadequate or poor quality sleep. *Acute insomnia*: transient, short term; *chronic insomnia*: primary. As with pain, insomnia is difficult to objectify. *Consequences*: fatigue, cognitive slowing, memory loss, poor work performance, diminished coping, intensified pain perception, lowered mood, anhedonia, accident proneness, compromised mental health.
- **Polysomnography Studies**: Normal sleep architecture consists of Rapid Eye Movement (REM) and Non-Rapid Eye Movement (NREM). REM consists of: low-amplitude brain wave activity; loss of muscle tone; muscle twitching; fluctuations in bp/pulse; dreaming, memory storage & creativity. Also involved in maintaining psychological “balance”. NREM sleep consists of 4 stages: (1)-transition from wake to sleep (latency); (2)-“natural sleep”; associated with changes in immune functions; (3)-; & (4)-“deepest sleep”. *Slow wave delta sleep*; physiologically most important component. Sleep normally proceeds through NREM 1-4, and returns to stage 2 before entering REM - about 70-90 minutes after sleep onset. REM & NREM alternate about 90 minutes apart. REM increases & delta sleep decreases as night proceeds. Stage 4 sleep decreases with age.
- **“Disorder of Initiating & Maintaining Sleep” (DIMS)**: Pt. characteristics: “light sleepers”; improved ability to sleep when away from their usual environment; overly concerned. *Factors*: *psychological* (high stress, “neurotic personality”, chronic, high anxiety); *physiological* (increased levels of arousal, increased polysomnographic abnormalities, but normal sleep architecture); *conditioned* (pt’s attempts to sleep, coupled to thoughts, attitudes, behaviors incompatible with sleep); *abnormal perceptions* (of sleep/wake state; over-estimation of degree of insomnia).
- **Insomnia in HIV**: results from disease stage, medical comorbidities, medications, or CNS complications. In HIV, there is often: shorter total sleep time; longer sleep onset (latency); reduced sleep efficiency; more frequent awakenings; more time awake; increased stage 1 & decreased stage 2. *Other factors*: the pt.’s sleep-wake cycle; normal circadian rhythm; age; life events; coping mechanisms; substance use; sleep hygiene; psychiatric illness. *“Remedies”*: 25% of pts with insomnia use OTC meds; 27% use ETOH; <15% use prescribed hypnotics. *Habitual short sleep duration* is associated with increased mortality. *HIV hypersomnia* is associated with fatigue in advanced disease and contributes significantly to morbidity.
- **DSM Differential**: primary insomnia/hypersomnia; narcolepsy; breathing-related sleep d/o’s; circadian rhythm sleep d/o; dyssomnia; parasomnia; major depression; generalized anxiety d/o; adjustment d/o; hypomania/mania; delirium/dementia; pain syndromes; medication side effects. *Substance-induced sleep disorders*: ETOH, cocaine, amphetamines, caffeine, nicotine, cannabis, heroin, opioids. *Medications*: prescribed antiretrovirals, interferon/interleukin, dapsone, amphotericin-b, INH, acyclovir, steroids, methylphenidate, bronchodilators, protease inhibitors, antihistamines, antiemetics, antidepressants, quinolones, zidovudine, lamivudine (3TC).
- **Medical Differential**: cardiovascular (CHF, PND, CAD, HPTN, arrhythmias); GI (GERD, PUD, hepatic failure); renal (RF, UTI, polyuria); endocrinopathies (DM, hypo/hyperthyroidism); unremitting pain; rheumatologic disease (arthritis, collagen vascular disease); pregnancy; neurologic d/o’s (delirium, TBI, CVA, myoclonus, MD, dementia, migraines, epilepsy); non-specific.
- **General Treatment Principles**: Educate the patient. Determine and address underlying etiology if possible. Treat generally if *specific* etiology cannot be determined. Ask pt. to use sleep log to assess sleep efficiency. Calculate *sleep efficiency* = time in bed (minus) time in bed awake (divided by) total time in bed X 100. (<85% suggests need for formal treatment.)
- **Non-Pharmacologic Interventions**: Teach good *sleep hygiene rules*: curtail time in bed; don’t “force” sleep, eliminate bedroom clock; exercise; avoid caffeinated beverages; alcohol and chocolate; regularize bedtime; eat a light bedtime snack; use relaxation tapes.
- **Pharmacologic Interventions**: 5 classes: *barbiturates* (avoid using); *benzodiazepines* [BZP’s] (use only those with shorter half-lives, only & warn against mixing with ETOH); *non-*

benzodiazepines; certain AD's (see also "Mood Disorders"); antihistamines (avoid using if possible); chloral derivatives (avoid using). Be alert to drug interactions (see also "Mood Disorders"). If a certain BZP is already being prescribed for anxiety, it may also be used for sleep, thus eliminating unnecessary "polypharmacy". If insomnia is due to depression, antidepressants will help, but may take 3-6 weeks to become effective.

- **Benzodiazepine Side Effects:** drowsiness, ataxia, incoordination, amnesia, syncope, liver dysfunction, granulocytopenia, rebound insomnia. Habituation, tolerance, physical dependence, withdrawal may occur. Pt.'s spelling "*trouble*" may be at higher risk of addiction (*transient, regressive, overanxious, unstable, bulimic, labile, episodes.*)

(see also "Anxiety Disorders" & "Mood Disorders" for medications & dosing recommendations)

Hypnotic BZPs	dose range/day	~elim. t ^{1/2}	met. pathway	Comments:.....
*(triazolam)	0.125-0.25mg/d	~2hrs	oxidation	anterograde amnesia, rebound insomnia
*temazepam	15-30mg/d	~12hrs	glucuronide conjugation	less likely to accumulate
flurazepam	has a long half-life of 40-150 hours, avoid			
quazepam	has a long half-life of 40+ hours, avoid			
estazolam	1-2mg/d	~12hrs	oxidation	

*frequently used for sleep promotion, but avoid *triazolam* if patient receives 3A4 inhibitors, including protease inhibitors

other BZP's:

*lorazepam	0.5-8mg/d	~13hrs	glucuronide conjugation	less likely to accumulate
oxazepam	30-120mg/d	~7hrs	glucuronide conjugation	less likely to accumulate
clonazepam	0.5-8mg/d	~25hrs	oxidation	
diazepam	2-60mg/d	~50+hrs	oxidation	
chlordiazepoxide	15-100mg/d	~50+hrs	oxidation	
alprazolam	0.25-4.0mg/d	~12hrs	oxidation	very difficult withdrawal

Other:

antihistamines	avoid if possible (anticholinergic)			
zolpidem	5-10mg/d	~2.5hrs		non-benzo; no tolerance, withdrawal
barbiturates	avoid			
chloral hydrate	avoid			

Benzodiazepines	"Safer" with 3A4 inhibitors	Avoid with 3A4 inhibitors
lorazepam	Safer	-----	
temazepam	Safer	-----	
oxazepam	Safer	-----	
alprazolam	-----	Avoid	
*triazolam	-----	Avoid	
estazolam	-----	Avoid	
midazolam	-----	Avoid	

- ♦ *Drug-interactions:* coumadin and disulfiram slow the metabolism of BZP's causing enhanced, prolonged effects; INH and estrogens exacerbate effects of BZP's through enzyme inhibition; rifampin and tobacco interfere with enzyme induction and may reduce BZP effects.