Treatment of Insomnia in Substance Abusing Patients

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Sleep disorders are highly prevalent—50 million US adults annually report having difficulty sleeping. In any given year, it is estimated that up to 10 million people consult a health care practitioner for sleep disorders, and of these, half receive prescriptions for sleep medications. Like other common conditions, insomnia results from many causes and varies widely in severity and duration from patient to patient. It is more prevalent in women, and its prevalence increases with age and socioeconomic class. It is more prevalent in patients with medical disorders and particularly in those with psychiatric or substance abuse disorders.

Sleep disturbances have many causes. Thus, clinicians should search for underlying situational stressors and psychiatric, medical, or pharmacologic causes, and treat insomnia as a symptom, accordingly. The duration of sleep difficulties is probably the most important guide to evaluation and treatment. Transient insomnia (no more than a few nights) and short-term insomnia (less than 2 to 3 weeks) usually occur in people with no history of sleep abnormalities. Long-term insomnia (more than 3 weeks) may be associated with a variety of conditions.

ETIOLOGY

Acute stress and environmental disturbances are probably the most common causes of transient and short-term insomnia. Pharmacologically induced insomnia can be caused by a number of psychotropic medications or drugs of abuse. Neuroleptics, for example, may cause akathisia, an extrapyramidal side effect characterized by anxiety and a sense of motor restlessness. Rebound or withdrawal insomnia may follow the abrupt discontinuation of some sedative-hypnotic agents, especially benzodiazepines with a short half-life. The use of stimulants, such as cocaine or amphetamines, or withdrawal from alcohol, may cause central nervous system excitation that leads to insomnia. For many substance abusing patients in recovery, increased caffeine and nicotine intake at night may cause trouble sleeping.

Chronic insomnia by definition lasts for at least 3 weeks. Between one third and two thirds of patients with chronic insomnia have a recognizable underlying psychiatric illness. It is estimated that 10% to 15% of patients with chronic insomnia have an underlying problem of substance abuse, especially of alcohol and other sedatives. Although alcohol in low-to-moderate amounts initially promotes sleep, it may ultimately disrupt and fragment sleep as a result of either partial tolerance and withdrawal during the night, or somatic effects (gastrointestinal upset, etc). Sleep may be disturbed for months or years in chronic abstinent alcoholics. Protracted withdrawal syndromes associated with discontinuation of long-term benzodiazepine or opiate use also typically include persistent insomnia.

GENERAL MANAGEMENT OF INSOMNIA

The general management of insomnia should initially involve identifying medical, psychiatric, or substance-related causes of insomnia and treating them appropriately. Clinicians should recognize that sleep disturbances are common features of many psychiatric disorders, including depression, mania, anxiety, stress-related reactions, and psychotic disorders. Sleep dis-
TABLE 1
Sleep Hygiene Techniques: Methods of Improving Sleep Habits

Try to establish a regular rising time in the morning. A regular sleeping pattern strengthens the
sleep/wake cycle and promotes a regular sleep-onset time.

Avoid coffee, cola, tea and chocolate after the evening meal.

Avoid heavy evening meals. A light snack or a warm drink before bedtime may promote sleep.

Wind down for a period before sleep time. Quiet activities, such as reading, relaxing in a hot bath, or meditating, help promote sleep.

Avoid using the bedroom for watching television, doing paperwork, eating or other activities. Bedrooms should be used only for sleeping or sexual activity.

If sleep does not occur after 30 minutes in bed, get up and engage in a quiet activity until sleepy again. A brief slow walk may be helpful.

Avoid taking naps during the day, especially in the evening.

Check the bedroom temperature. Temperatures that are too hot or too cold interfere with sleep. Reducing the noise level is also helpful in creating an environment conducive to sleep.

Engage in gentle exercise to produce fatigue before sleep. Heavy exercise should be avoided just before retiring, because it delays sleep.

Restrict fluids in the evening and before retiring, to help reduce the frequency of awakening to go to the bathroom.

Turbulence can contribute significantly to the physical, psychologic, social, emotional, and vocational impairment of the patient. In clinical settings, it is important to recognize and treat the underlying disorder primarily, rather than treating insomnia exclusively as a symptom. Mood stabilizers, sedating antidepressants, and low-potency neuroleptics may all be useful for managing insomnia as a symptom of a respective disorder. Many non-pharmacologic therapies have been used in the treatment of chronic insomnia, including progressive muscle relaxation, biofeedback techniques, guided imagery, meditation, sleep restrictive therapies—and probably most universally important—sleep "hygiene" techniques.6,7 (Table 1).

In addition, insomnia is almost universally a feature of alcohol or drug withdrawal, and may stem in part from psychological factors, in addition to physiologic dysregulation. Sleep disturbances often represent emergence of repressed anger or veiled sadness or grief that surfaces during detoxification and early recovery from addiction. The expression and tolerance of these emergent affects, rather than the customary impulse to block them, is an important part of the recovery process. Three cases are briefly shown, which illustrate some of the complexities of insomnia seen within the context of addiction.

In a case vignette from "The AA Member: Medications and Other Drugs," a report from a group of physicians in AA (1984, New York: Alcoholics Anonymous World Services) "Ann's Story" concludes with "one night, in deep emotional pain over a broken engagement, I popped a sleeping pill and vividly remember feeling just as drunk as I had ever been on liquor. . . . I learned once and for all that I was not capable of handling any mood-altering drug." The pamphlet later goes on to suggest that it becomes clear that just as it is wrong to enable or support any alcoholic to become readdicted to any drug, it's equally wrong to deprive any alcoholic of medication that can alleviate or control other disabling physical or emotional problems. AA, which does not usually take a position on anything, seems to be trying to help their members avoid sedative-hypnotics while countering a lay opinion in AA that medications for affective disorders and psychoses are suspect.

In a second case,10 a corporate executive presented at age 38 with a 2-year history of fulminate alcoholism featuring missing days at work because of hangovers, being drunk at work, and suffering cognitive impairment from chronic intoxication. There was a dramatic absence of any ability to feel angry. Severe insomnia ensued for the first 3 years of his psychoanalysis. His associations were initially emotionless, but as he processed past experiences of abuse and abandonment, he was able to tolerate and express his affects. Return of the ability to sleep normally was accompanied by an ability to experience anger consciously.

A third case is a follow-up of another psychoanalysis of a man with alcoholism, previously reported.11 The patient had persistent obsessive ruminations about various psychosocial stressors and he drank at bedtime to induce sleep. At his request, he was begun on fluoxetine 20 mg per day. Four weeks later he reported, "I was exhausted, and I knew I was going to have a hard time sleeping. I lay in bed, and thought of having a drink. You know how it goes, all these issues suddenly come to mind. My heart starts pounding and my chest muscles bunch together.
I started my meditation exercises. And you know what? I thought of issues, but I didn’t seem to get stuck on them. I stopped obsessing and moved on. I fell asleep. 

The risk of relapse must be weighed against non-treatment. Clinical experience suggests that persistent insomnia may sometimes lead to relapse in a recovering patient via efforts to self-medicate with alcohol, benzodiazepines, or opiates. The treating clinician must decide on a tactical basis whether 12-step, dynamic, behavioral, or psychopharmacologic interventions are most likely to be efficacious. More than one of these treatment modalities will often be combined.

MEDICATION MANAGEMENT

Administration of various agents for the relief of insomnia is not a modern innovation. Since ancient times, various remedies have been used to induce and maintain sleep. By the 1970s, benzodiazepines had replaced barbiturates and other more toxic hypnotics as primary treatment modalities. Although effective hypnotics, barbiturates, and barbiturate-like drugs are considered far less safe than benzodiazepines, having lower therapeutic-to-toxic ranges, greater synergism with alcohol, and greater lethality in overdose. 

Barbiturate-like drugs

The barbiturate-like hypnotic drugs choral-hydrate, methyprylon, and ethchlorvynol have the same risks as barbiturates and no specific advantages. The most popular, choral hydrate, exerts its hypnotic action within 30 minutes and is converted to an active metabolite that has a half-life of 4 to 14 hours. Its effects are markedly potentiated by alcohol, and it forms the basis for “knock-out drops” or a “Mickey Finn.” The usual therapeutic dose of choral hydrate is 500 to 1000 mg, but the reported lethal dose of choral hydrate may be as low as 5 to 10 grams. In light of the present availability of numerous safer effective hypnotic agents, the use of barbiturate-like drugs is almost never clinically indicated.

Benzodiazepines

For the general population, benzodiazepines have become the primary medications prescribed for treatment of transient to short-term insomnia. For the most part, they are safe and efficacious, working almost immediately. Although all benzodiazepines have hypnotic activity, only estazolam, flurazepam, quazepam, temazepam, and triazolam are labeled for use as hypnotics in the United States. Fatal overdose is rare with any oral benzodiazepine unless it is taken with alcohol or other central nervous system depressants. The effectiveness of benzodiazepines as hypnotics can persist for weeks or even months, but all benzodiazepines can produce tolerance and physical dependence and withdrawal phenomena, especially with higher dosage and longer duration of treatment.

Benzodiazepines generally shorten sleep latency, although there is considerable inter-agent and inter-individual variance in efficacy as a result of differences in absorption, lipophilicity, elimination half-life, and metabolism. Benzodiazepines prolong the first two stages of sleep and shorten stages three and four and REM sleep. Stages three and four are considered deep or restorative sleep stages, and deprivation of REM sleep may lead to agitation or aggressive behavior.

Advantages and disadvantages of the benzodiazepine hypnotic agents may depend on dose and half-life of the particular agents. Long-acting benzodiazepines may maintain sleep throughout the night, but often lead to daytime sedation, “hangover,” and impaired performance. Short-acting agents may result in early morning awakening or drug-induced anterograde amnesia. Both have been reported to cause rebound insomnia following discontinuation.

No studies have demonstrated the hypnotic efficacy of benzodiazepines beyond 12 weeks. Furthermore, in studies involving a parallel placebo group, no differences between active medication and placebo after two to three weeks of treatment were noted. There is evidence that shorter-acting, high potency agents such as triazolam and lorazepam may lose their sleep-promoting properties within 3 to 14 days of continuous use.

Schneider-Helmert investigated the effects of continuous, long-term benzodiazepine use (6 months to years) in patients with chronic insomnia. Compared with drug-free insomniacs, benzodiazepine users were found to have loss of hypnotic effectiveness and substantial suppression of delta slow-wave and REM sleep. Subjective perceptions of hypnotic efficacy were not confirmed via objective measurements (polysomnography). For instance, those patients on benzodiazepines reported an average overestimation of sleep of 72 minutes per night. On drug withdrawal, they reported, on average, a 61 minute over-estimation of sleep-onset latency. Schneider-Helmert concluded that long-term users’ overestimation of sleep while taking a benzodiazepine, coupled with their awareness of persistent sleep disturbance on discontinuation, may explain why some patients develop “low-dose dependence.” Citing the findings of Lucki et al that with regular use benzodiazepine-impaired memory functions persist for a period following discontinuation, Schneider-Helmert speculate that overestimation of sleep time may be the result of drug-induced anterograde amnesia.

Benzodiazepines may offer temporary symptomatic relief for transient and short-term insomnia. They are generally not recommended for long-term treatment, as primary treatment for chronic insomnia, or for patients with sleep apnea. Furthermore, most addiction medicine specialists believe that it is unwise to treat abstinent alcoholics with benzodiazepines or barbiturates, because they are cross-tolerant with alcohol.
### TABLE 2
Overview of EEG Sleep Effects of Antidepressant Therapies

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<thead>
<tr>
<th>Drug</th>
<th>Continuity</th>
<th>SWS</th>
<th>REM</th>
<th>Sedation</th>
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<tr>
<td>Tricyclics</td>
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<td>Amitriptyline</td>
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<td>Desipramine</td>
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<td>Clomipramine</td>
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<td>Monoamine Oxidase Inhibitors</td>
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<td>Phenelzine</td>
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<td>Transylcypromine</td>
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<td>Selective Serotonin Reuptake Inhibitors</td>
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<td>Venlafaxine</td>
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<td>Serotonin Receptor Modulators</td>
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<tr>
<td>Trazodone</td>
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<td>Nefazodone</td>
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= no change; ↓ = decreased; ↑ = increased; + = slight effect; ++ = small effect; +++ = moderate effect; ++++ = great effect; - = no significant effect. ND= no data available; REM= rapid eye movement sleep; SWS= slow-wave sleep.


### Antidepressants

The various antidepressant drugs now available exert differing effects on arousal states and sleep architecture (Table 2). For example, even when administered in the morning, a significant incidence of insomnia has been reported with all of the selected serotonin reuptake inhibitors (SSRIs). In sleep laboratory studies, disruption of sleep architecture has been observed in subjects taking these medications. Studies of both fluoxetine and paroxetine reveal increased sleep latency, increased REM latency, increased wakefulness, and decreased overall sleep efficiency. Tertiary tricyclic antidepressants (TCAs), such as amitriptyline or doxepin, are generally sedating due to their affinity for H1-histamine receptors. They are thus predominately administered at bedtime, to take advantage of this side effect, or so as not to impair daytime performance. TCAs may also cause substantial anticholinergic side effects, orthostatic hypotension, and cardiac conduction effects that limit their use. As measured via polysomnography, TCAs tend to increase duration of non-REM sleep (especially stage 1 and 2), suppress REM and prolong REM latency, but may decrease nocturnal awakenings. These effects begin with the start...
of therapy and often at low doses. REM rebound may occur, however, when TCA therapy is discontinued. Monoamine oxidase inhibitors (MAOIs) may cause more pronounced REM suppression, increase REM latency, cause REM rebound, and have numerous other problematic side effects.  

Trazodone, a heterocyclic antidepressant, increases sleep continuity quite dramatically and is often used in combination with SSRIIs to counteract SSRI-induced insomnia. Compared with tricyclics, trazodone is much safer in overdose and has virtually no cardiac side effects, and fewer anticholinergic side effects, and is less likely to cause orthostatic hypotension. It is generally well tolerated. Trazodone may have prolonged effects, however, and lead to daytime sedation or a "hangover" feeling. Clinical experience suggests that with low dose titration and attention to inter-individual variance in time of nightly administration, it is an effective hypnotic alternative to benzodiazepines. Male patients receiving trazodone should be warned about the rare occurrence of priapism.

A newer antidepressant, nefazodone, is a combined 5-HT1A and 5-HT2 receptor blocker which is similar to trazodone, but a bit less sedating. It is unusual in that it seems to increase REM sleep time, in contrast to most other antidepressants. Nefazodone reportedly has very little effect on other stages of sleep and increases sleep continuity without causing daytime sedation. It also reportedly causes very few other side effects or problematic drug interactions and is thus well tolerated by most patients. Table 2 summarizes effects of various antidepressants on the sleep cycle. Mintazepine is another new antidepressant with reported sedative effects; however, clinical data regarding sleep stage effects are not yet available.

Imidazopyridines

Imidazopyridines are hypnotic agents with a chemical structure unrelated to benzodiazepines, barbiturates, or other classes of drugs with known hypnotic properties. Although chemically unrelated to the benzodiazepines, they do bind to benzodiazepine receptors in the brain and share some of the pharmacokinetic properties of benzodiazepines. In contrast to benzodiazepines, which bind non-selectively to benzodiazepine receptors (of which three subtypes have been identified), imidazopyridines appear to bind selectively to the GABA-BZ complex. Zolpidem is the only imidazopyridine currently marketed in the United States. Mean peak plasma concentration occurs approximately 1.6 hours after ingestion and elimination half-life ranges from 1.5 to 4 hours and is dose-dependent. The recommended adult dose is 10 mg. In patients with impaired liver function, dosing must be reduced in the elderly and in patients with impaired liver function.

Zolpidem has two innovative features: unlike the benzodiazepines, it does not decrease stages three or four or REM sleep, and tolerance or withdrawal symptoms do not appear to occur. Zolpidem has little effect on the stages of sleep, and few, if any, anxiolytic, anti-convulsant, or muscle-relaxant effects. Results of a 3 week trial of more than 1700 subjects showed that zolpidem significantly decreased time to sleep onset and significantly increased total sleep time without causing significant adverse events. However, long-term trials are lacking, and next day drowsiness, dizziness, and rebound insomnia have been reported. Synergistic effects with benzodiazepines and alcohol have also been observed, as have reports of vivid dreams or nightmares.

Seven cases of zolpidem-induced psychotic reactions or sensory distortions have been reported in the literature. The common features of these reported cases are that all the patients were female, all reactions occurred at dosages of 10 mg or more per day (suggesting a dose-dependent effect), the reactions usually appeared 20 to 30 minutes after dosing, and most of the reactions resolved within minutes to hours.

Most sleep experts believe that zolpidem has little potential for abuse because high doses cause a high incidence of nausea and vomiting. The drug has, however, been classified as a schedule IV controlled substance, like the benzodiazepines. Zolpidem appears fairly safe when taken alone in overdose, but deaths have occurred when patients took zolpidem with other drugs that depress the central nervous system.

Non-Prescription Hypnotics

Diphenhydramine, hydroxyzine, doxylamine, and some other antihistamines are sometimes used as hypnotic agents and are currently approved by the FDA for sale as non-prescription sleep aids. They are not as potent as benzodiazepines, and most cause troublesome anticholinergic side effects such as dry mouth. Tolerance to hypnotic effects appears to develop rapidly. Melatonin might turn out to be helpful in promoting sleep, but adequate controlled trials are lacking, and the purity of the products now available in the US, the hypnotic dose, and the adverse effects of taking the hormone are all unknown. Tryptophan, another weak natural hypnotic agent, is no longer available for prescription due to its association with eosinophilia myalgia; thus, its use cannot be recommended until further evidence establishes its safety.

Conclusion

Insomnia is a common sequela of numerous medical and psychiatric conditions, and is often associated with substance abuse disorders or early abstinence. Traditionally, benzodiazepines have been the primary medications used to treat insomnia. A review of the literature supports recommendations that sleeping pills are indicated only for the temporary symptomatic relief of transient and short-term insomnia in the context of a doctor-patient rela-
relationship and in combination with nonpharmacologic treatment. Even within these parameters, however, initial improvement is often limited, and tolerance eventually develops. As benefits dissipate over time, emergence of side effects makes risk-to-benefit ratios prohibitive. In substance abusing patients or patients in recovery from substance abuse, benzodiazepines have a great potential for tolerance, dependence, and abuse and are thus usually contraindicated. Zolpidem, because it binds to the same GABA receptor as benzodiazepines, albeit more selectively, may well show the same liability for abuse (psychologically, if not physiologically) as benzodiazepines. Neurochemical, electrophysiologic, and clinical research data support the efficacy of non-addictive medications as preferential for use in substance abusing patients. Until further experience is forthcoming, nefazodone or trazodone remain the recommended first line agents for treatment of insomnia in patients with addictive disorders who do not respond adequately to non-medication interventions.

REFERENCES

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