Pharmacologic Treatment Dilemmas Among Patients With Addiction

Written by Brian Hoyle

An American Psychiatric Association symposium dealt with pharmacologic dilemmas in the treatment of addiction.

INSOMNIA

Kirk J. Brower, MD, University of Michigan Health System, Ann Arbor, Michigan, USA, discussed the treatment of insomnia among patients with substance use disorders. Alcoholics frequently and persistently experience problems sleeping [Zhabenko N et al. *Clin Exp Res* 2012], which can drive relapsed drinking [Malcolm R et al. *J Clin Sleep Med* 2007] and even suicidal tendencies [Klimkiewicz A et al. *Drug Alcohol Depend* 2012]. Abstinence is no guarantee that insomnia will end soon, with a return to normal sleep requiring months to several years depending on the aspect of sleep [Brower K et al. *Am J Addictions* 2011; Brower K. *Alcohol Res Health* 2001]. Contributing factors to insomnia include substances or medications, premorbid insomnia, co-occurring disorders (medical, psychiatric, other), environmental factors, and inadequate sleep hygiene.

In alcohol-dependent patients who are suffering from insomnia, the clinician should always assume that alcohol is a responsible factor but be cognizant that it may not be the only factor. So, reduction in drinking, preferably abstinence, is a necessary and reasonable first-line treatment. Reducing or eliminating alcohol may not be a complete answer, since those dependent on alcohol can have other psychiatric and medical disorders associated with insomnia, as well as sleep disorders such as sleep apnea and periodic limb movements, and can be experiencing increased stress. These other factors can be most productively addressed by behavioral therapy, pharmacotherapy, or both.

A sleep diary can be useful in assessing sleep patterns. A diary kept for several weeks early in treatment can also help the clinician evaluate the patient and delay prescribing medications that might prove to be unwarranted. Validated sleep questionnaires, including the Sleep Problems Questionnaire and the Insomnia Severity Index, can be useful assessment instruments. Nonprescription sedatives, including antihistamines and supplements (eg, melatonin, valerian), are popular but lack evidence-based rigor. Medications approved by the United States Food and Drug Administration (FDA) are benzodiazepine receptor agonists, ramelteon, and doxepin. Dr. Brower cautioned against using benzodiazepine receptor agonists, since no randomized controlled trials involving postwithdrawal insomnia among alcoholics have been published and because of the possibility of drug abuse and overdose in combination with alcohol and other medications. While studied, the data on trazodone, quetiapine, and gabapentin are not sufficiently robust to recommend these drugs.

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ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Frances R. Levin, MD, Columbia University Medical College, New York, New York, USA, discussed the pharmacologic treatment of attention-deficit/hyperactivity disorder (ADHD) among patients with substance use disorders. ADHD that is diagnosed during childhood can persist into adulthood and has been linked to increased substance use disorder in this population [Kessler RC et al. *Am J Psychiatry* 2006]. Identification and treatment of ADHD among substance abuse patients is important (Table 1).

Several treatments have been recommended for co-occurring substance use disorders and ADHD. Atomoxetine is a first-line treatment, particularly for abstinent alcohol-dependent patients [Wilens TE et al. *Drug Alcohol Depend* 2008]. Bupropion is used off-label and is not FDA approved for ADHD [Mariani JJ, Levin FR. *Am J Addiction* 2007]. Modafinil and tricyclic antidepressants

Table 1. Importance of Attention-Deficit/Hyperactivity Disorder Among Substance Abusers Seeking Treatment

Earlier onset of substance use disorder in the presence of attention-deficit/hyperactivity disorder
Reduced chance of remission if dependency develops
Higher relapse rates among adolescents and adults
Longer time to achieve remission
More treatment exposure, yet less treatment success
Higher rates of other psychiatric comorbidities

are also used off-label. Guanfacine is on-label for ADHD. Stimulants can be used but cautiously and only when indicated [Schubiner H. *CNS Drugs* 2005]. Frequent patient monitoring for adverse side effects is necessary [Wilson JJ, Levin FR. *J Child Adolesc Psychopharmacol* 2005]. Nonpharmacologic adjunctive therapies include cognitive-behavioral therapy and group or individual psychotherapy [Wilens TE. *Psychiatr Clin North Am* 2004].

The risk of misuse or diversion (ie, selling) of medications prescribed for ADHD is a reality that clinicians need to be aware of. Attention paid to "red flags" of misuse or diversion is prudent (eg, patient demand for particular medication, repeated lost prescriptions, discordant pill count). The goal is to achieve a balance between the risk of undertreatment and that of misuse or diversion.

ALCOHOL

Kathleen Brady, MD, PhD, Medical University of South Carolina, Charleston, South Carolina, USA, discussed alcohol pharmacotherapy. Alcohol dependence is heterogeneous, and identifying the subtype is paramount for gainful therapy (Table 2).

Table 2. Characteristics of Alcohol Subtypes

Type A	Chronologically later onset
	Less severe dependence
	Less antisocial personality
	More anxiety, depression
Type B	Chronologically early onset
	More severe dependence
	Greater antisocial personality disorder

The FDA-approved medications include disulfiram, naltrexone, and acamprosate. However, the key to pharmacotherapy is compliance. This is problematic for chronic diseases in general and alcohol treatment in particular, given that <50% of patients take medications as prescribed and 40% to 60% relapse within a year [McLellan AT et al. *JAMA* 2000]. A long-acting injectable formulation of naltrexone that sustains plasma levels of the opioid antagonist for a month reduced the frequency of heavy drinking in a study involving >600 subjects [Garbutt JC et al. *JAMA* 2005]. A randomized controlled trial that compared the effects of naltrexone and acamprosate (alone or in combination) among 1383 subjects reported the benefit of the former for reducing drinking [Anton RF et al. *JAMA* 2006].

Glutamate directly stimulates the release of dopamine. The influence on associative learning may have benefits in behavioral changes that reduce drinking. The antiseizure drug topiramate, which potentiates GABA-ergic transmission, appears effective in reducing episodes of heavy drinking [Johnson BA et al. *Lancet* 2003]. Other GABA-ergic/glutamatergic agents that are being assessed are baclofen, vigabatrin, and gabapentin.

OPIOID USE DISORDERS

Hilary S. Connery, MD, PhD, Harvard Medical School, Boston, Massachusetts, USA, discussed the selection of opioid agonist and antagonist therapies. The approach is safe and can double the success rate of opioid abstinence. Paramount among the variety of symptoms is anxiety, which can drive relapse and discontinuation of treatment. Opioid withdrawal can also be harmful among pregnant women, people with cardiovascular difficulties, and patients with diabetes, for example.

Opioid medications act differentially. The μ-opioid receptor antagonists (naltrexone, naloxone) and agonists (buprenorphine, methadone) and the α-2 adrenergic receptor agonist clonidine are used in the early stage of opioid withdrawal. The goal of treatment then becomes maintenance of abstinence. Drugs used here include naltrexone extended release, buprenorphine/naloxone tablet or suboxone film, and methadone.

μ-Opioid receptor agonists can be commenced immediately as a means of weaning a subject off opioids but require a prescription and are given in a clinic setting. A lapse or termination of medication will lead to opioid withdrawal. Antagonists are given when a subject is opioid-free. This delay to treatment can increase chance of relapse, which can increase the risk of opioid overdose. Other important aspects of treatment are diet, exercise, and other forms of stress reduction. The overriding aim is to maintain treatment.