

PHARMACOTHERAPY OF ADOLESCENT ALCOHOL AND OTHER DRUG USE DISORDERS

RAMON SOLHKHAH, M.D., AND TIMOTHY E. WILENS, M.D.

Medications are playing an increasingly important role as adjuncts to psychosocial strategies of alcoholism treatment. Although problems associated with the use of alcohol and other drugs (AODs) often appear in adolescence, most studies of AOD pharmacotherapy have been conducted in adults. Because youth may react differently from adults to both the therapeutic and potentially harmful effects of medications, the applicability of existing data to youth who abuse AODs remains unclear. This article explores strategies for using medications to treat AOD use disorders¹ in youth, focusing on alcoholism when relevant data are available.

A systematic search of published research revealed 10 studies on the effects of medication for treating children or adolescents with AOD disorders. The studies differ significantly in experimental methods and in the definition and measurement of treatment outcome. Two were controlled studies, a type of study that compares the effects of the experimental medication with those of a sham medication, or placebo. Four were open trials, which evaluate experimental medication without a placebo control. Four were case reports, which describe the responses of one or a few patients to specific treatments. Treatment outcomes were evaluated using patient questionnaires; random urine screens to detect AOD use; and overall ratings of improvement in the patient's addictive behavior, co-occurring psychiatric symptoms, and psychosocial functioning. Although uncontrolled studies and case reports may suggest directions for research, controlled studies are needed to evaluate the effects of a medication.

Pharmacotherapeutic strategies for treating AOD disorders, as described in this sidebar, include craving

reduction, substitution therapy, aversive therapy, and treatment of underlying psychiatric conditions (Kaminer 1995). Because subjects in all the studies discussed received concurrent nonpharmacological treatment, this article describes effects presumably attributable to the medications themselves.

Craving Reduction

Many researchers consider craving a fundamental aspect of addiction. Various definitions of craving exist based on behavioral, neurological, and subjective psychological criteria. In this article, the term "craving" refers to the urge or desire for a particular AOD. Craving can be evaluated experimentally by behavioral responses in laboratory animals or by self-reported mental states in human subjects. The reduction of craving through pharmacotherapy may help prevent relapse in patients undergoing treatment for alcoholism or other addictions.

Among the best known medications for treating alcoholism is naltrexone (ReViaTM or Trexan[®]). Naltrexone blocks certain communication pathways in the brain that are involved in the development of addiction to both alcohol and abused opiates (e.g., heroin). In studies of alcohol-dependent adults, naltrexone decreased alcohol consumption by approximately one-half (Volpicelli et al. 1997). The only study on the use of naltrexone in AOD-abusing youth is a case report of a 17-year-old alcohol-dependent male who remained abstinent during a brief (30-day) trial of naltrexone (Wold and Kaminer 1997). Nalmefene (a naltrexone derivative) and acamprostate also show promise for reducing alcohol craving in adults (Gastfriend et al. 1998). The efficacy of those medications in adolescents has not been determined.

Additional medications that may modify AOD craving include serotonin reuptake inhibitors (SRIs) and tricyclic antidepressants (e.g., desipramine [Norpramin[®]]), which are used to treat some psychiatric conditions in both adult and juvenile patients (Wilens et al. 1998). Studies of SRIs to reduce craving for cocaine, opiates, and alcohol in adults yielded mixed results (Gastfriend et al. 1998). In case reports,

RAMON SOLHKHAH, M.D., is a fellow in child and adolescent psychiatry at Massachusetts General Hospital and McLean Hospital and a Clinical Fellow in Psychiatry at Harvard Medical School, Boston, Massachusetts.

TIMOTHY E. WILENS, M.D., is director of Substance Abuse Services in the Clinical Research Program in Pediatric Psychopharmacology at Massachusetts General Hospital and an associate professor of psychiatry at Harvard Medical School, Boston, Massachusetts.

¹AOD disorders considered here include addiction (i.e., dependence) and abuse.

desipramine administration led to overall functional improvement in cocaine-dependent adolescents (Kaminer 1994), possibly by treating patients' underlying psychiatric disorders (see the section entitled "Treatment of Underlying Psychopathology").

Substitution Therapy

In substitution therapy, the patient's drug of abuse is replaced with the supervised administration of a related medication. Substitution therapy is predicated on the assumption that replacing AODs with prescribed medications will shift control of AOD use to the patient and clinician while reducing the patient's need to maintain behaviors associated with addiction (e.g., illicitly obtaining drugs). An established treatment for opiate dependence in adults is its replacement by methadone, a synthetic opiate that unlike heroin, causes minimal euphoria, drowsiness, or depression. Unfortunately, no systematic data exist on opiate substitution in adolescents, and Federal regulations severely restrict the use of methadone in youth (Gastfriend et al. 1998).

Research suggests that cocaine dependence may possibly be treated by substitution therapy using psychostimulants. Those medications differ from cocaine in chemical structure but have some behavioral and emotional effects in common with it. The psychostimulant methylphenidate (Ritalin®) either led to no change or decreased cocaine use in adults with and without co-occurring psychiatric disorders (specifically attention deficit/hyperactivity disorder) (Grabowski et al. 1997; Levin et al. 1997) (see article by Wilens, pp. 127–130). The extrapolation of those findings to cocaine-abusing youth remains unstudied.

No substitution therapies exist for alcohol. However, the use of medications during alcohol detoxification is predicated on a similar concept. The brain adapts to

heavy or prolonged alcohol consumption by developing tolerance to some of alcohol's effects. The mechanisms of tolerance to alcohol-induced sedation may contribute to the symptoms of nervous system hyperactivity that occur when alcohol consumption suddenly ceases (i.e., withdrawal).² Diazepam (Valium®) and related sedative medications (i.e., benzodiazepines) alleviate withdrawal symptoms in adults. Therefore, despite a lack of systematic experimental data, adolescents manifesting alcohol withdrawal symptoms are often treated with benzodiazepines.

Aversive Therapy

The goal of aversive therapy is to reduce AOD use through medications that lead to unpleasant responses following the consumption of the abused drug. In the United States, aversive treatment for alcoholism generally involves disulfiram (Antabuse®). This medication interferes with the body's metabolism of alcohol, resulting in the accumulation of a toxic by-product called acetaldehyde. Alcohol consumption in the presence of disulfiram results in flushing, nausea, vomiting, headache, and chest discomfort; less commonly, it results in chest pain, palpitations, difficulty breathing, dizziness, confusion, and low blood pressure (Gastfriend et al. 1998; Myers et al. 1994). Rare serious reactions can include irregular heartbeat, heart failure, respiratory depression, seizures, and death. Alcohol consumption may produce those effects for up to 2 weeks after the patient has stopped taking disulfiram.

In a case study, Myers and colleagues (1994) administered disulfiram (250 milligrams daily) to two alcohol-dependent adolescents. One subject remained abstinent for 4 months before discontinuing disulfiram and relapsing to alcoholism. The other subject failed to take the medication and continued drinking. The problem of noncompliance with treatment suggests that disulfiram may be most useful in residential (i.e., inpatient) treatment facilities (e.g., for use on weekend passes).

*Adolescents
manifesting alcohol
withdrawal
symptoms are often
treated with
benzodiazepines.*

²Withdrawal symptoms include anxiety, tremors, increased heart rate and, in some cases, convulsions.

Disulfiram should be administered, under supervision, only to patients who are medically healthy, intellectually competent, insightful about their AOD problem, and highly motivated to achieve recovery.

Treatment of Underlying Psychopathology

Evidence suggests that some people may use AODs in part to self-medicate distressing mental states associated with underlying psychiatric conditions (Khantzian 1997). Adolescents with AOD disorders exhibit a high prevalence of psychiatric disorders compared with the general population (see article by Clark and Bukstein, pp. 117–126). Disorders that co-occur with AOD abuse include depressive and anxiety disorders, bipolar disorder, attention deficit/hyperactivity disorder (ADHD) (see article by Wilens, pp. 127–130) and conduct disorder³ (Bukstein et al. 1989; Weinberg et al. 1998). Few studies exist on the pharmacological treatment of those conditions in AOD-abusing youth.

Findings from open trials suggest that the psychostimulant pemoline (Cylert[®]) and the antidepressant bupropion (Wellbutrin[®] and others) may ameliorate symptoms of ADHD in AOD-abusing youth with co-occurring conduct disorder.

Because those studies were completed in inpatient settings, however, effects on AOD use were not determined (Leon et al. 1998; Riggs et al. 1996). Methylphenidate improved both AOD disorders and co-occurring ADHD in adolescents and young adults (Grabowski et al. 1997; Levin et al. 1997; Riggs 1998).

Mood disorders in youth are among the most difficult of psychiatric disorders to treat. In a small open trial (Riggs et al. 1997), the SRI fluoxetine (Prozac[®]) reduced depressive symptoms in adolescents with AOD disorders while producing no significant adverse side effects. Bipolar disorder is characterized by marked mood swings that range from severe depression to a state of abnormal mental excitement and physical energy (i.e., mania). In adolescents, mania is generally manifested by aggressivity and behavioral outbursts.

Medications for bipolar disorder include lithium; certain anticonvulsants, such as carbamazepine (Tegretol[®]), valproic acid (Depakote[®]), and gabapentin (Neurontin[®]); and antipsychotic medications, such as thioridazine (Mellaril[®]) and olanzapine (Zyprexa[®]) (Wilens et al. 1998).

Patterns of AOD abuse among bipolar youth suggest an attempt to self-medicate manic symptoms. Results of recent research are consistent with this possibility. In controlled trials, Geller and associates (1998) administered lithium to adolescents with comorbid bipolar and AOD use disorders. After 6 weeks of treatment, lithium-treated subjects exhibited significant reductions in AOD use compared with subjects administered a placebo. Decreased AOD use correlated with improvements in overall functioning consistent with increased stability of mood. Similarly, adolescents subject to temper outbursts and irritability reduced their marijuana consumption after their moods were stabilized with valproic acid (Donovan et al. 1996).

*Clinicians
should monitor
patients' progress
by objective
measures.*

Safety and Monitoring

Appropriate pharmacotherapy for adolescent AOD use disorders depends on the medication's effectiveness, potential for abuse, possible interactions with other medications or AODs, and factors that affect patient compliance (e.g., unpleasant side effects). The risks of pharmacotherapy are highlighted by a recent report of an adverse drug interaction between marijuana and tricyclic antidepressants (Wilens et al. 1997). In addition, a systematic assessment of a nonresidential child psychiatry clinic revealed that 25 percent of adolescent AOD-abusing patients were entirely noncompliant with pharmacotherapy and 8 percent had abused their prescribed medication or had made it available to others for illicit use (Wilens et al. 1996). Clinicians should therefore monitor patients' progress by objective measures whenever possible. For example, blood tests may be used to confirm whether the patient is taking prescribed doses of medications, and frequent random urine screens may detect illicit AOD use.

Research results, coupled with clinical experience, suggest the importance of tailoring the choice of medication and the course of treatment and followup to the

³For definitions of psychiatric syndromes, see article by Clark and Bukstein, pp. 117–126.

needs of the individual patient. Coordination of pharmacotherapy with family members and other caregivers can enhance treatment outcome. Additional controlled studies are essential to assess the effectiveness and safety of pharmacotherapy both alone and in combination with other addiction interventions. ■

References

- BUKSTEIN, O.G.; BRENT, D.A.; AND KAMINER, Y. Comorbidity of substance abuse and other psychiatric disorders in adolescents. *American Journal of Psychiatry* 146:1131–1141, 1989.
- DONOVAN, S.J.; SUSSER, E.S.; AND NUNES, E.V. "Changes in Marijuana Use in Teenagers with Temper Outbursts and Irritable Mood After Successful Treatment with Open-Label Depakote." Paper presented at the 58th Annual Meetings of the College on Problems of Drug Dependence, San Juan, Puerto Rico, June 1996.
- GASTFRIEND, D.; ELMAN, I.; AND SOLHKHAH, R. Pharmacotherapy of substance abuse and dependence. *Psychiatric Clinics of North America: Annual of Drug Therapy* 5:211–229, 1998.
- GELLER, B.; COOPER, T.; SUN, K.; ZIMMERMAN, B.; FRAZIER, J.; WILLIAMS, M.; AND HEATH, J. Double-blind and placebo controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. *Journal of the American Academy of Child and Adolescent Psychiatry* 37:171–178, 1998.
- GRABOWSKI, J.; ROACHE, J.D.; SCHMITZ, J.M.; RHOADES, H.; CRESON, D.; AND KORSZUN, A. Replacement medication for cocaine dependence: Methylphenidate. *Journal of Clinical Psychopharmacology* 17:485–488, 1997.
- KAMINER, Y. Cocaine craving. *Journal of the American Academy of Child and Adolescent Psychiatry* 33:592, 1994.
- KAMINER, Y. Issues in the pharmacological treatment of adolescent substance abuse. *Journal of Child and Adolescent Psychopharmacology* 5:93–106, 1995.
- KHANTZIAN, E.J. The self-medication hypothesis of substance abuse disorders: A reconsideration and recent applications. *Harvard Review of Psychiatry* 4(5):231–244, 1997.
- LEON, S.L.; RIGGS, P.D.; COFFMAN, L.M.; AND MIKULICH, S.K. An open trial of bupropion for ADHD in adolescents with conduct disorder and substance use disorder. (Abstract) *Problems of Drug Dependence 1997: Proceedings of the 59th Annual Scientific Meeting of the College on Problems of Drug Dependence, Inc.* NIDA Research Monograph 178. NIH Pub No. 98–4305. Washington, DC: U.S. Govt. Print. Off., 1998. p. 252.
- LEVIN, F.R.; EVANS, S.M.; MCDOWELL, D.; AND KLEBER, H.D. Methylphenidate treatment for cocaine abusers with adult attention-deficit/hyperactivity disorder: A pilot study. *Journal of Clinical Psychiatry* 1–21, 1997.
- MYERS, W.; DONAHUE, J.; AND GOLDSTEIN, M. Disulfiram for alcohol use disorders in adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry* 33:484–489, 1994.
- RIGGS, P. Clinical approach to treatment of ADHD in adolescents with substance use disorders and conduct disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 37:331–332, 1998.
- RIGGS, P.D.; THOMPSON, L.L.; MIKULICH, S.K.; WHITMORE, E.A.; AND CROWLEY, T.J. An open trial of pemoline in drug dependent delinquents with attention deficit hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 35:1018–1024, 1996.
- RIGGS, P.; MIKULICH, S.; COFFMAN, L.; AND CROWLEY, T. Fluoxetine in drug-dependent delinquents with major depression: An open trial. *Journal of Child and Adolescent Psychopharmacology* 7:87–95, 1997.
- VOLPICELLI, J.R.; RHINES, K.C.; AND RHINES, J.S. Naltrexone and alcohol dependence. *Archives of General Psychiatry* 54:737–743, 1997.
- WEINBERG, N.; RAHDERT, E.; COLLIVER, J.; AND GLANTZ, M. Adolescent substance abuse: A review of the past 10 years. *Journal of the American Academy of Child and Adolescent Psychiatry* 37:252–261, 1998.
- WILENS, T.; BIEDERMAN, J.; ABRANTES, A.; AND SPENCER, T. "Naturalistic Treatment of Psychiatrically Referred Adolescents with a Substance Use Disorder." Paper presented at the Annual Proceedings of the American Academy of Addiction Psychiatry, San Francisco, California, December 1996.
- WILENS, T.E.; BIEDERMAN, J.; AND SPENCER, T.J. Case study: Adverse effects of smoking marijuana while receiving tricyclic antidepressants. *Journal of the American Academy of Child and Adolescent Psychiatry* 36:45–48, 1997.
- WILENS, T.; SPENCER, T.; FRAZIER, J.; AND BIEDERMAN, J. Psychopharmacology in children and adolescents. In: Ollendick, T., and Hersen, M., eds. *Handbook of Child Psychopathology*. New York: Plenum Publishing, 1998. pp. 603–636.
- WOLD, M., AND KAMINER, Y. Naltrexone for alcohol abuse. *Journal of the American Academy of Child and Adolescent Psychiatry* 36:6–7, 1997.

influences on the onset of heavier drinking among adolescents. *Journal of Studies on Alcohol* 59:311–317, 1998.

ROHDE, P.; LEWINSOHN, P.M.; AND SEELEY, J.R. Psychiatric comorbidity with problematic alcohol use in high school students. *Journal of the American Academy of Child and Adolescent Psychiatry* 35(1):101–109, 1996.

SANTOS, A.B.; HENGGELER, S.W.; BURNS, B.J.; ARANA, G.W.; MEISLER, N. Research on field-based services: Models for reform in the delivery of mental health care to populations with complex clinical problems. *American Journal of Psychiatry* 152(8):1111–1123, 1995.

STEWART, S.H. Alcohol abuse in individuals exposed to trauma: A critical review. *Psychological Bulletin* 120(1):83–112, 1996.

TARTER, R., AND VANYUKOV, M. Alcoholism: A developmental disorder. *Journal of Consulting and Clinical Psychology* 62(6):1096–1107, 1994.

ZUCKER, R.A. The four alcoholisms: A developmental account of the etiologic process. In: Rivers, P.C., ed. *Alcohol and Addictive Behavior*. Lincoln: University of Nebraska Press, 1987. pp. 27–83

National Alcohol Screening Day

April 8, 1999

Mark your calendar now!

On April 8, 1999, the first National Alcohol Screening Day (NASD) will provide free public outreach, education, and screening for alcohol problems at locations across the United States.

Screening sites include college campuses, hospitals, treatment centers, and mental health clinics.



For more information, to locate the site nearest you, or to volunteer to assist with this special event, visit the NIAAA Web site (www.niaaa.nih.gov or www.nmisp.org).

NASD is a program of the National Mental Illness Screening Project in collaboration with the National Institute on Alcohol Abuse and Alcoholism (NIAAA). NASD is made possible through support from NIAAA, with additional funding from the American Psychiatric Foundation, Charter Behavioral Health Systems, and unrestricted educational grants from Eli Lilly and Company and Solvay Pharmaceuticals, Inc. Leading organizations in the field supporting NASD also include the American Medical Association, the American Academy of Addiction Psychiatry, American Psychiatric Association, American Psychological Association, American Society of Addiction Medicine, Mothers Against Drunk Driving, and the National Organization on Fetal Alcohol Syndrome.