Use of Pharmacologic Agents in the Treatment of Addiction

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This article describes the use of pharmacologic agents in the treatment of addictive disorders, summarizing present practice and efforts to develop new agents for future use. Although this discussion is limited to three commonly abused substances—alcohol, opiates, and cocaine—it is important to note that there is progress regarding treatment of dependence on two other drugs, nicotine and benzodiazepines. Physicians are now prescribing agonist modalities to treat dependence on the most frequently used and deadliest addicting drug—nicotine. Research is under way to evaluate the role of other medications to help smokers initiate abstinence and avoid relapse.1

Also, several important studies have described the phenomenology of dependence on benzodiazepines, the most frequently prescribed group of drugs.2

Finally, this article does not address the pros and cons of using pharmacologic agents per se as treatment modalities for addictive disorders. Large numbers of proponents advocate “drug-free therapies” for treatment of addicts and maintain that medications are countertherapeutic. Indeed, nonpharmacological therapies such as educational interventions, counseling or psychotherapy, and self-help groups are treatments, whereas pharmacological agents are drugs. The role of such agents is clearly adjunctive to other treatments. Further research efforts will help to better distinguish subgroups of addicts for whom pharmacotherapy is indicated and contraindicated.

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ALCOHOLISM

Liskow and Goodwin3 have categorized six classes of drugs used in the treatment of alcoholism4.
Agents for alcohol withdrawal;  
Anticraving agents;  
Aversive agents;  
Agents for psychiatric problems concomitant to alcoholism;  
Agents for concurrent alcohol and drug abuse problems;  
Amethystic agents.

Agents for Alcohol Withdrawal

It is interesting to note that controversy persists regarding the existence and incidence of the alcohol withdrawal syndrome, which encompasses a highly variable gamut of symptoms. Symptoms extend from relatively mild, such as sweating, tachycardia, hypertension, tremors, and anxiety, to more serious phenomena such as convulsions and delirium. Hypothesized origins of the syndrome are disturbances in several neuronal systems. Growing clinical consensus is that clinicians should routinely consider adjunctive pharmacologic therapy for alcoholic withdrawal in order to limit the severity of subsequent withdrawal episodes.

Benzodiazepines are the most commonly used agents to treat alcohol withdrawal. These agents act by several methods. They bind to a benzodiazepine receptor in order to facilitate the action of gamma-aminobutyric acid (GABA). In addition, benzodiazepines act on both the noradrenergic system and the hypothalamic-pituitary-adrenal axis to diminish the severity of arousal in these systems.

Diazepam is the most commonly used benzodiazepine to treat alcohol withdrawal and is usually administered at 5 mg, four times per day. An alternate method of dosage is the “loading dose” method in which 5 mg diazepam is given every one to two hours to a patient until withdrawal symptoms subside, at which time the drug is discontinued. The long half-life of diazepam provides continuing coverage and limits the need for further administration of medication.

Another commonly used long-acting benzodiazepine for alcohol withdrawal is chlordiazepoxide.

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Since diazepam and chlordiazepoxide are metabolized in the liver, there may be problematic accumulation. Because of this factor there is growing use of short- and intermediate-acting benzodiazepines such as oxazepam and lorazepam. These agents do not accumulate in the body for as long a period as the long-acting benzodiazepines, and a clinician can readily administer a more specific dose. Because of the problem of dependency on benzodiazepines in alcoholics, routine use of benzodiazepines should be restricted to treating the alcohol withdrawal syndrome.

β-adrenergic blockers (atenolol and propranolol) may have a future role in treating alcohol withdrawal. However, a troubling side effect of β-adrenergic blockers is delirium and hallucinations.

Other agents being examined in clinical trials for treatment of alcohol withdrawal include the α-adrenergic agonists, clonidine and lofepridine; a dopamine blocker, haloperidol; calcium channel antagonists or blockers, such as nifedipine; and carbamazepine, a tricyclic anticonvulsant. Litien and Allen point out that use of these medications for alcohol withdrawal remains experimental except in situations where a clinician is treating target symptoms such as hallucinations (haloperidol) or seizures (carbamazepine).

Anticraving Agents

Agents that directly attenuate drinking behavior are being studied. These drugs include serotonin uptake inhibitors (fluoxetine, fluvoxamine, citalopram, vialdaline, and zimelidine), dopamine agonist (bromocriptine), a GABA receptor agonist (bis acetyl homotaurine), and narcotic antagonists (naltrexone and nalozone). Although these agents are in various early stages of efficacy studies, there has been progress toward understanding the role of serotonin uptake inhibitors in the treatment of alcoholism. The mechanism of action of serotonergic agents has not yet been clarified, but one method may be by decreasing appetitive behaviors for alcohol. Another method may be by production of a strong taste aversion to alcohol.

Aversive Agents

Disulfiram (Anlabase), usually administered as a 250-mg oral tablet once a day to an abstinent patient, is the most widely used and studied aversive agent. Disulfiram inhibits a liver enzyme, aldehyde dehydrogenase, and thus leads to increased blood levels of acetaldehyde, the first metabolic product of ethanol metabolism. An increased level of acetaldehyde causes the toxic effects of the disulfiram-ethanol reaction, during which a patient taking disulfiram experiences tachycardia, flushing, palpitations, dyspnea, nausea, vomiting, and headache.

Patient factors that yield good prognosis for treatment with disulfiram are age more than 40 years, high motivation for abstinence, social stability, nondepressed mood, compulsive personality traits, and the ability to form dependent relationships with counselors or clinics. Efficacy studies of disulfiram have had considerable methodological problems, including lack of blinded condition, adequate control groups or sample size, and rigid exclusion criteria, which limit the generalizability of the findings.

Patient compliance has been the troublesome clinical problem with disulfiram. Noncompliance has been addressed by efficacy studies.
using behavior therapy or subcutaneous implantation of disulfiram. Behavior therapy interventions, such as the development of contingency paradigms involving a spouse or significant other person, do appear to increase patient compliance with disulfiram. However, studies of subcutaneous disulfiram implantation have shown problems of erratic blood levels of disulfiram because of a variable release pattern. Despite these limitations, disulfiram is a frequently used pharmacological adjunct in the treatment of alcoholism.

Agents for Concurrent Psychiatric Disorders

Addictive disorders are frequently associated with psychiatric comorbidity such as mood, anxiety, personality, and other substance use disorders. Moreover, psychiatric comorbidity affects prognosis for recovery. Although depressive symptoms have been associated with alcoholism, little is known regarding the efficacy of various tricyclic antidepressant medications (imipramine, desipramine, ami-triptiline, and doxepin) and the course of alcoholism. Litten and Allen point out that there are various subtypes of depression associated with alcoholism—primary, secondary associated with chronic intoxication, and detoxification or withdrawal depressive symptoms.

The antidepressant and serotonin uptake inhibitor, fluoxetine, may have a role in treatment of alcoholism beyond its antidepressant properties. Studies with lithium, a drug used to treat manic-depressive illness, have produced conflicting results. Studies with the nonbenzodiazepine, nondependence-producing drug, buspirone, have been promising with reports of decreased craving for alcohol, lower anxiety scores, and fewer treatment dropouts compared to placebo. However, results of these studies must be viewed cautiously by clinicians until other clinical trials are completed.

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Agents for Concurrent Alcoholism-Drug Addiction

Regarding use of medications to treat alcoholics with associated drug use, methadone is the only drug for which there are data and consensus. Methadone maintenance for opiate addicts is advised during treatment for alcoholism. Although depressive symptoms have been associated with alcoholism, little is known regarding the efficacy of various tricyclic antidepressant medications (imipramine, desipramine, amitriptyline, and doxepin) and the course of alcoholism. Litten and Allen point out that there are various subtypes of depression associated with alcoholism—primary, secondary associated with chronic intoxication, and detoxification or withdrawal depressive symptoms.

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Agonist Maintenance Agents

Methadone hydrochloride, a synthetic opiate developed in Germany during World War II, has become a commonly employed adjunct to counseling for many opiate addicts since the early 1960s. Opiate addicts request treatment after being addicted for several years and having led highly dysfunctional lives during this time. They have not only become physically dependent on opiates, but, often as a consequence of addiction, have limited social, employment, and interpersonal skills.

Administration of methadone, when offered in an adequate dose within the context of a clinical setting of individual counseling, peer group support, urine toxicology, and medication pick-up schedules contingent on stability and progress, offers an opportunity for addicts to gain stability, break free of a drug abuse lifestyle, and prepare themselves for subsequent detoxification. However, many patients productively remain on methadone maintenance for years.

Opiate Detoxification

Detoxification of opiate addicts is performed by gradual reduction of an opiate dose over several days or weeks. Because of its long half-life, one may switch an opiate addict to methadone and then withdraw it gradually. Other agents that have been used to detoxify opiate addicts are clonidine, an α2 agonist that suppresses opioid-dependent hyperactivity in the locus coeruleus, and clonidine combined with naltrexone, an orally administered opioid antagonist, which competes with opioid agonist at opioid receptor sites with a greater affinity for receptors. Another opioid antagonist, naltrexone, is administered intravenously in order to reverse opiate intoxication or overdose. Studies of clonidine have shown mixed results in detoxification efficacy, but
studies of clonidine combined with naltrexone have shown greater promise because the time for withdrawal is considerably reduced.\textsuperscript{14}

**Opiate Antagonist Maintenance**

As part of an aftercare program, the opioid antagonist naltrexone serves to make euphoric effects of opiates nonavailable to recovering opiate addicts who might have access to opiates. Although naltrexone is mistakenly perceived to be an "Antabuse" for opiate addiction, naltrexone does not produce aversive effects. Rather it serves to block or reverse opiate effects, including euphoria. Although results of clinical trials with naltrexone are mixed, naltrexone maintenance requires a level of motivation by patients and has been found to work optimally in the context of family support, counseling, and external contingencies.\textsuperscript{19}

**Other Agents**

Two other drugs have shown promise in the treatment of opiate addiction. Levo-alpha-acetyl methadol (LAAM) has pharmacological effects like methadone, but its onset is slower and duration of its effects is longer. LAAM has the advantage of suppressing opioid withdrawal symptoms for 48 to 72 hours. This property is an advantage to clinics and patients because patients need to be medicated only three days per week rather than seven days as with methadone.\textsuperscript{14}

Finally, buprenorphine, a partial-opiate agonist currently approved as a parenteral analgesic, has shown promise as an alternative drug to methadone for treating opiate addiction. Because of its partial-opiate antagonist properties, buprenorphine exhibits reduced agonist activity with increasing doses and has a less severe withdrawal syndrome after prolonged use.\textsuperscript{14} Clinical efficacy trials are presently under way with buprenorphine. Patients on heroin or methadone have been transferred to buprenorphine and then detoxified. Results of these studies are being examined as regards buprenorphine’s utility as a detoxification agent as well as its effects on concurrent heroin and cocaine use during maintenance and detoxification.\textsuperscript{14}

**COCAINE**

Cocaine has emerged in the past two decades as a major drug of abuse. Although psychosocial and residential treatments have proved to be efficacious, treatments have been nonspecific and labor-intensive. Because of the incidence of cocaine abuse and the need for more specific, efficacious, and cost-effective treatments, results of efficacy studies of several pharmacological agents are found in samples of cocaine addicts seeking treatment.

Weiss and Mirin\textsuperscript{16} have divided proposed agents to treat cocaine addiction into four major classes:

- Drugs that block the effects of cocaine (antagonists);
- Drugs that produce an aversive reaction if taken in combination with cocaine;
- Drugs that treat premonobid coexisting psychiatric disorders;
- Drugs that treat cocaine-induced states such as intoxication, withdrawal, and craving.

However, at present, there exists no clearly efficacious pharmacological intervention for cocaine addiction, nor is there any drug approved for such use by the federal Food and Drug Administration (FDA).

**Cocaine Antagonists**

Drugs that are purported to block cocaine euphoria include imipramine, bromocriptine, trazodone, and neuroleptic drugs such as haloperidol. In addition, there have been animal and human studies with lithium and buprenorphine. Results of these studies to date are not encouraging.

**Cocaine Aversive Agents**

Little research has been accomplished with cocaine aversive agents. Similarly, few studies are available to evaluate the efficacy of drugs used to treat premonobid coexisting psychiatric disorders in cocaine addicts, although investigators have examined desipramine, lithium, magnesium pemoline, and methylphenidate.\textsuperscript{16}

**Agents for Cocaine-Induced States**

Most research regarding pharmacological agents to treat cocaine addiction have focused on cocaine-induced states such as detoxification, or "withdrawal," and craving during the initial few weeks of abstinence from cocaine. Studies have been performed with desipramine, imipramine, bromocriptine, amantadine, carbamazepine, and flupenthixol decanoate. Of these agents, desipramine has been the most promising; however, results of studies with desipramine are mixed.

At best, desipramine appears to modestly increase periods of abstinence and decrease craving for cocaine in the early phase of outpatient treatment. Desipramine has not been shown to affect attrition in outpatient treatment, nor has it been shown to decrease relapse to cocaine abuse.\textsuperscript{16} At this point, more research is needed to specify subgroups of cocaine addicts who may benefit from desipramine.\textsuperscript{17} Two inpatient studies\textsuperscript{18,19} of short-term abstinence phenomenology in cocaine addicts have demonstrated that symptoms after inpatient cessation of uncomplicated cocaine addiction are relatively mild and decrease linearly. Findings do not support use of pharmacological agents in the inpatient management of routine detoxification from cocaine.\textsuperscript{19}
SUMMARY

There are drugs that are commonly used as adjunctive treatment modalities for patients with addictive disorders. For alcohol abuse and dependence, agents include benzodiazepines for alcohol withdrawal and disulfiram as an aversive agent to prevent relapse. For opiates, methadone is administered as an adjunct to treatment; naloxone and naltrexone are used to intervene with intoxication, assist with detoxification, and prevent relapse to opiate use during abstinence. At this time, there are no acceptable pharmacological interventions for cocaine addiction. Promising drugs that may ultimately prove useful include serotonergic uptake blockers for alcoholism, LAAM and buprenorphine for opiate addiction, and dopamine uptake inhibitors for cocaine addiction.

Clearly, progress has been achieved during the past decade regarding pharmacotherapy for alcohol and drug addiction. Not only have studies of pharmacologic agents for addictive disorders provided data regarding safety and efficacy, they have also provided insights into phenomenology of addictive disorders.

Negativity efficacy outcome studies of pharmacotherapeutic agents, while disappointing, often provide data to investigators regarding the course, pathophysiology, and natural history of an addictive disorder. Additional research regarding use of pharmacological agents as adjunctive treatment modalities for addictive disorders is needed and will be forthcoming.

REFERENCES