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A Range of Research-Based Pharmacotherapies for Addiction

Charles P. O'Brien

Modern approaches to the treatment of addiction have been influenced by several important factors. These include advances in our understanding of the nature of addiction based on longitudinal studies, and progress in elucidating the biological underpinnings of addictive behavior. In addition, changes in the system for delivery of services have begun to shape the way that addiction is treated.

Addiction used to be defined as tolerance to and physical dependence on a drug of abuse. Tolerance represents an adaptation to repeated exposure to a drug such that the pharmacological response is diminished (*1*). Physical dependence is a state manifested by withdrawal symptoms when drug-taking is terminated or significantly reduced. Withdrawal symptoms tend to be a quasi "rebound" opposite in direction to the initial drug effects, which begin as the drug disappears from the body through metabolism and excretion (*2*). If tolerance and withdrawal symptoms were the only problems of addicts, "treatment" would consist of detoxification, a process that allows the body to cleanse itself while the individual receives medication to block withdrawal symptoms (*2*). If drug-taking does not resume, homeostatic mechanisms will gradually readapt to the absence of the drug (*3*). We now know that detoxification is, at best, a first step in beginning treatment and that achieving the drug-free state is not a particularly significant accomplishment. The more difficult aspect is prevention of relapse to drug-taking behavior.

It is important to note that tolerance and withdrawal symptoms occur commonly among nonaddicts who are treated with any of the common medications to which the body adapts. These include medications for high blood pressure, for anxiety, and for pain. Indeed, the fear of producing "addiction" leads to the undertreatment of pain (*4*) even in terminal cancer patients and may indirectly fuel the debate in the United States over physician-assisted suicide. Many patients are allowed to suffer needlessly when effective pain relief is available, because of the fear of addiction; thus, suicide may appear to be the only alternative (*5*).

If tolerance and physical dependence are not the core of addiction, then what is the preferred definition? As the definition has evolved (*1*), addiction is a syndrome characterized by compulsive drug-seeking behavior that results in an impairment in social and psychological functions or damage to health. Whereas initial drug use is voluntary, the individual, once addicted, is beset by nearly irresistible urges to continue or to resume drug-taking. Even after detoxification and long periods of abstinence, relapse frequently occurs despite sincere efforts to refrain. People or situations previously associated with drug use produce involuntary reactions and may provoke a relapse (*6*). The biological mechanisms for these apparent reflex patterns are suggested by data from animal models at the neurochemical level [see a review by Koob and Le Moal (*7*), this issue] and the molecular level [see a review by Nestler and Aghajanian and (*8*), this issue]. At the clinical level, these behavior patterns are manifested by repeated return to drug-taking behavior that is often patently self-destructive. A key point for the clinician to realize is that the proneness to relapse is based on changes in brain function that continue for months or years after the last use of the drug. Of course, these changes in brain function interact with environmental factors such as social stress and situational triggers.

Confusion about the diagnosis and prognosis of addiction stems from the fact that by the time an addicted person presents for treatment, there are numerous complicating social and psychological problems that frequently overshadow the addiction process. The typical patient evolves from drug user, to abuser, to dependent or addicted person over a period of years. During this time it is common for social, occupational, family, medical, and legal problems to develop. The Addiction Severity Index (*9*) contains seven classes of variables that are assessed in order to obtain a severity rating. Those patients who rank at the severe level only on quantity of drugs used and not on other dimensions have a reasonably good prognosis. In contrast, those with severe psychosocial complications scoring high in the nondrug areas have a poor prognosis and are likely to relapse regardless of their level of drug use severity (*10*).

Psychiatric disorders commonly coexist with addictive disorders. These include anxiety disorders, psychotic disorders, and affective disorders such as depression. Although some of these so-called "dual diagnosis" cases

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are simply a coincidental occurrence of common disorders, the overlap is greater than would be expected by chance on the basis of population prevalences (*11*). There are two kinds of possible relations, and both probably occur in different groups of drug users. A preexisting psychiatric disorder could increase the likelihood of initiating drug use as an attempt at "self-medicating" the psychiatric symptoms (*12*). A second possibility is that chronic drug-taking could produce changes in the brain and in social interactions that predispose an individual to the development of psychiatric disorders. This latter hypothesis is supported by the observation that many of the psychiatric symptoms associated with addictive disorders begin after the addictive process and resolve spontaneously after several weeks of abstinence from drugs of abuse (*13*). If they do not resolve, these associated psychiatric disorders must be treated with specific psychoactive medications.

As our understanding of the chronic nature of addictive disorders has developed, it has become apparent that treatment should be based on a chronic disease model such as that used for diabetes or asthma rather than modeled on treatment for an acute disease such as pneumonia. The shift from acute or short-term treatment to a chronic model is still in process, and there is resistance to this change. In the United States, the health care system has traditionally paid for detoxification but not for long-term relapse prevention.

Medication Categories

The notion of treating a drug problem with a medication was controversial in the past, and there are still those who are philosophically opposed (*14*). If one accepts the evidence that chronic drug use produces lasting changes in the brain, it is natural to look for medications that can combat the effects of the "lesion" and facilitate behavioral treatment approaches (*15*). Behavioral treatments are still necessary to deal with psychosocial aspects of the disorder, but the two approaches can work together. Research efforts have produced medications for treating patients dependent on opioids, nicotine, and alcohol (*16*). These medications are presented below according to their treatment category and mechanism. Medications may aid in detoxification and in the prevention of relapse. Although there are interesting developments in the search for medications to be used in the treatment of dependence on cocaine or other stimulants, nothing so far has become available. For stimulants, hallucinogens, inhalants, or cannabinoids, the available treatments are behavioral, and medications are used only if a coexisting psychiatric disorder is present (*16*).

Detoxification

Paradoxically, although addiction is a chronic disorder, detoxification may be the only element covered in some health insurance programs. Detoxification is very useful as a beginning treatment for nicotine dependence (*17*). The discomfort of withdrawal can be relieved by gradually reducing doses of nicotine delivered by skin patch, chewing gum, or nasal spray. After facilitating detoxification, nicotine is sometimes used for several months as a maintenance treatment to block craving and to aid the former smoker to remain abstinent (*17*).

In the treatment of alcohol-dependent patients, detoxification is very important because the withdrawal syndrome is potentially life-threatening (*18*). There is evidence that sensitization occurs so that repeated withdrawals become progressively more severe, but treatment of withdrawal symptoms may retard the sensitization process (*19*). Benzodiazepines effectively suppress the withdrawal syndrome, and with proper attention to electrolytes and vitamins, the vast majority of patients can be safely eased into the alcohol-abstinent state in preparation for a long-term rehabilitation program (*19*).

For patients dependent on heroin and other opioids, medically aided detoxification is only helpful in preparation for long-term, drug-free or opioid-antagonist-maintained rehabilitation (*2*). Because most patients relapse quickly in drug-free programs, detoxification, although supported by public and private healthcare delivery systems, is often useless (*20*). Detoxification is not applicable for those opioid-dependent patients who prefer maintenance with methadone or another opioid agonist (*21*). Long-term, drug-free therapeutic communities can be effective for selected patients, but they are expensive and increasingly unavailable (*22*).

The opioid withdrawal syndrome, though uncomfortable, is not life-threatening, and it can easily be treated by gradually decreasing doses of a long-acting opioid such as methadone (*20*). When methadone for detoxification is unavailable because of legal restrictions, medications that suppress central adrenergic activity have been found to be useful (*20*). The latter medications were developed with animal models of opioid withdrawal. These studies demonstrated that alpha-2 agonists acting at autoreceptors produced presynaptic inhibition of locus coeruleus activity, effectively reducing the large adrenergic component of opioid withdrawal (*23*). Thus, clonidine (*23*) and lofexidine (*24*) have found a place in the clinic for treating the symptoms of opioid withdrawal. The withdrawal syndrome from stimulants such as cocaine or amphetamine consists of tiredness and depressive symptoms that usually resolve over several days and do not require specific medication (*2*).

As a chronic disorder, addiction requires long-term treatment that is usually measured in months and years. The types of medication that have shown efficacy along with behavioral treatment in the prevention of relapse can be classified as agonists, antagonists, agonist-antagonist combinations, and anticraving medications.

Agonist Medications

The landmark demonstration in the 1960s that methadone is useful in the treatment of heroin addiction opened the way for the medical treatment of addictive disorders (*25*). Methadone is a slow-onset, long-acting mu opiate receptor agonist that reduces the craving for heroin and largely prevents the reward or euphoria if the patient "slips" and takes a dose of an opiate (*26*). The mechanism for preventing euphoria is called cross tolerance. It is based on the principle that tolerance (insensitivity) acquired by the use of one drug in a category conveys tolerance to all drugs in that category. Of course, the maintenance dose of methadone must be adjusted to the purity of heroin the individual was using. A dose of heroin significantly higher in opioid equivalents than the maintenance dose of methadone would override the cross tolerance effect (*26*). On a properly adjusted dose of methadone, patients can be maintained for many years (*27*). Craving for opioids is diminished or absent, and patients are able to engage in constructive activities (*26*). Cognition and alertness are not impaired, and functioning at complex tasks including higher education can be accomplished (*28*). Currently about 115,000 former heroin addicts are being maintained on methadone (*29*). Those with significant psychosocial problems require counseling or psychotherapy in addition to the medication. A newly available agonist that can be used for maintenance is levo-alpha acetyl methadyl (LAAM). This drug has long-acting metabolites that block withdrawal and craving for more than 72 hours and needs to be taken only two to three times per week. Another new medication, buprenorphine [not yet approved by the U.S. Food and Drug Administration (FDA)] is a partial agonist at the mu receptor and an antagonist at kappa receptors (*30*). As a partial agonist, buprenorphine produces limited opiate effects and, thus, overdose is rare. Because of its affinity for the mu receptor, buprenorphine effectively prevents the effects of other opi-

ates and opioids, thus reducing the likelihood that heroin will be used. Patients treated with buprenorphine become dependent on it as with methadone and LAAM, but the withdrawal symptoms from buprenorphine are quite mild.

Antagonists

Advances in understanding how opioids interact with opiate receptors to produce their pharmacological effects led to the development of specific antagonists that have a high affinity for these receptors but do not activate the chain of cellular events producing opioid drug effects (*31*). Naltrexone is an antagonist with high affinity for mu opiate receptors and less affinity for delta and kappa opiate receptors (*32*). Unlike methadone, it has no agonist effects, so there is no opioid calming or other subjective effects (*31*). When first introduced, naltrexone was thought to be an ideal medication for heroin addiction because it occupied opiate receptors and blocked the effects of subsequent heroin injections. Experience has shown that most heroin addicts prefer methadone treatment because it provides mild opioid reinforcing effects absent in naltrexone. Thus, naltrexone has been used very little except for "white collar" opioid addicts such as physicians and nurses and former addicts released from prison on probation (*33*). Less than 10% of those given this drug experience nausea and dysphoria (*34*). Although long-term blockade of opiate receptors might be expected to produce impairment of neuroendocrine function, remarkably few effects have been noted even in patients who have taken naltrexone daily for several years (*35*). There is reason to believe that a slow-release, injectable preparation of naltrexone would be more useful because it could be administered on a monthly basis, thus overcoming the problem of compliance when orally ingesting the medication (*36*).

Agonist-Antagonist Medications

An interesting combination that has shown efficacy in clinical trials is the combination of nicotine and mecamylamine to prevent relapse to smoking. It was hypothesized that stimulation of receptors by both an agonist and an antagonist would be more effective and the side effects from the two drugs would tend to cancel each other (*37*). Although the clinical data so far have been supportive of the hypothesis, the mechanism is unknown and more studies are needed.

Anticraving Medications

The concept of drug craving has been criticized because it is a subjective phenomenon that may have different meanings depending on the context. Craving may be elicited by cues previously paired with drug use or drug effects, but this cue-elicited craving may or may not lead to drug use (*38*). Recently the FDA approved the antidepressant bupropion as a medication that reduces craving for nicotine and may aid in preventing relapse to nicotine dependence even in the absence of depressive symptoms (*39*). The mechanism of action is unknown, but the results under double-blind conditions are clinically significant in decreasing the desire for nicotine and increasing the number of patients able to remain abstinent. A dual-medication approach can now be implemented with the nicotine patch to block withdrawal symptoms during detoxification and continuing with bupropion to reduce craving, thus aiding in the maintenance of the nicotine-free state.

An FDA-approved medication is also available to aid in the prevention of relapse to alcoholism. Double-blind studies have shown both a reduction in alcohol craving and significantly less relapse to alcoholic drinking in detoxified alcoholics treated with naltrexone (*34*, *40*). How an opiate receptor antagonist came to be found useful in the treatment of alcoholism is a tribute to the utility of animal models in the search for medications to treat addictive disorders. Beginning in the 1980s, blocking of opiate receptors was found consistently to reduce alcohol preference in studies with nonhuman primates and rodents. Figure 1A illustrates the first published study (*41*) that led Volpicelli and colleagues (*34*) to test the effects of naltrexone in human alcoholics (Fig. 1B). There are now human data suggesting that alcohol is less rewarding when opiate receptors are blocked, presumably because alcohol activates the endogenous opioid system (*42*). As of 1997 this medication is used as an adjunct in the rehabilitation of only a minority of alcoholics, but its efficacy is gaining in recognition, and its use for the treatment of alcoholism exceeds that for heroin addiction, the original reason for its development (*43*). Nalmefene, another long-acting opiate receptor antagonist used in the treatment of opioid overdose has also been reported to reduce alcohol relapse (*44*).

The usefulness of naltrexone in alcoholism was discovered in North America (*34*), and several European countries have already approved its use (*43*). Acamprosate, a completely different medication that appears to decrease desire for alcohol was developed in Europe (*45*) and is just beginning clinical trials in the United States. Acamprosate appears to reduce the long-lasting neuronal hyperexcitability that follows chronic alcohol use (*45*). The mechanisms are unclear but may include alterations in excitatory amino acid receptor gene expression. This medication suppresses the intake of alcohol in rats (*46*), and, as in the case of naltrexone, activity in the animal model predicts clinical efficacy. In double-blind studies (*47*), acamprosate has been shown to increase the likelihood of continuous abstinence in alcoholics and to shorten the period of

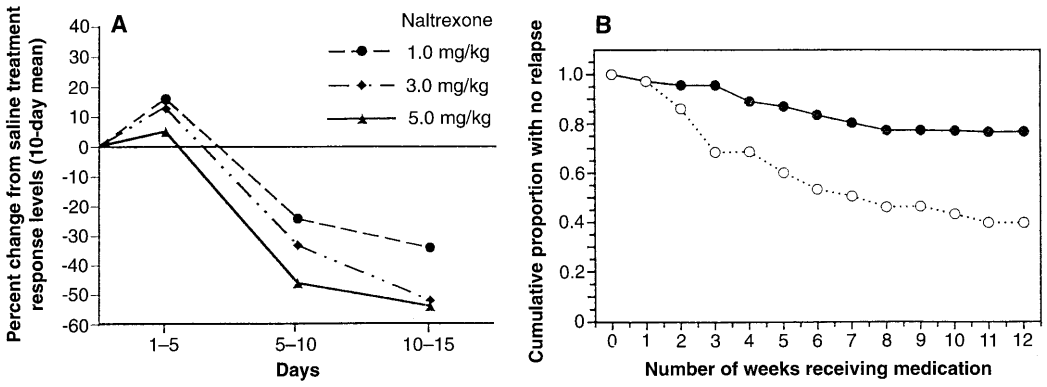

Fig. 1. A blockade of opiate receptors reduces alcohol self-administration. (**A**) Naltrexone pre-treatment produces a dose-dependent decrease in intravenous alcohol self-administration. Data are mean values from eight rhesus monkeys from (*41*). These data and others stimulated clinical studies, such as the one in (B). (**B**) The proportion of alcoholics not relapsing over 12 weeks of out-patient rehabilitation. Placebo group (open circles) shows significantly greater relapse to alcoholism than those randomized to naltrexone (filled circles). Data are from (*34*).

drinking if the patient has a "slip" and consumes some alcohol. Because acamprosate does not act on the endogenous opioid system, it is likely that its effects would be additive to those of naltrexone. Studies to test the interaction of these two medications are now planned.

Medication that Blocks Alcohol Metabolism

Until 1995, the only medication available to treat alcoholism was disulfiram. This medication blocks the metabolism of alcohol, causing the accumulation of acetaldehyde, a noxious by-product (*2*). The resulting acetaldehyde reaction is so unpleasant that it effectively prevents patients from consuming any alcohol. This drug still has a place in the pharmacopoeia of medications for alcoholism, but its usefulness is limited because patients do not like to take it and thus the majority simply do not comply with the prescription (*48*). Various techniques involving contracting or legal coercion have been described to improve compliance, and these have significantly improved the results of treatment (*49*).

Vaccines in Addictive Disorders

The notion of preventing relapse to drug dependence by immunizing the patient against the desired drug was first examined for morphine. Monkeys were immunized with morphine-6-hemisuccinate-BSA, and the resultant morphine antibodies were found to reduce self-administration of heroin, but not of cocaine (*50*). The technique was never tested in clinical trials, possibly because naltrexone became available as a specific antagonist that blocked the effects of all opioids at the receptor site rather than only those for which there were specific antibodies. Recently the technique has been applied to cocaine. Active immunization with a new, stable cocaine conjugate suppressed locomotor activity and stereotyped behavior in rats induced by cocaine but not by amphetamine (*51*). Brain concentrations of cocaine were also lowered by the antibodies, and in another study (*52*) rats were found to reduce intravenous cocaine self-administration after passive transfer of cocaine antibodies. More behavioral studies in animals involving dose-response relations are indicated because there are serious problems still to be addressed. Cocaine is very cheap and available in the United States. Patients who wish to relapse may be able to easily overwhelm the available antibodies by a high dose of the drug or simply take a different stimulant.

The U.S. Health Care System and Addictive Disorders

The efficacy of specific treatment approaches for addictive disorders is surprisingly good, and comparable with the results found with other chronic disorders such as diabetes or asthma (*53*). The controlled studies determining efficacy are conducted in academic institutions and may not reflect the effectiveness in average community treatment programs that are less well staffed. The problem of poorly trained clinicians is a serious one. Basic research has made important advances in understanding addiction, and this has already led to treatment advances. The present challenge is to make these advances generally available to patients in need.

Theoretically, treatment of substance use disorders should be a high priority for the health care system if for no other reason than because this treatment is clearly cost-effective. Substance abuse is known to be an important etiologic factor in many costly conditions such as cancer, liver failure, heart disease, accidents, and violence to name just a few. Several studies have shown that for every $1.00 invested in the treatment of substance abuse, there are cost savings of $4 to $12 (*54*) depending on the type of drug and the type of treatment. Unfortunately, the cost savings are long-term effects, and the profit-oriented world of managed care appears to focus on short-term goals. In the United States, funding for treatment of addictive disorders has been seriously curtailed in both public and private programs. When funding is available, it tends to be focused on brief treatments for addiction rather than long-term care of the chronic relapsing condition (*53*). Because of the low levels of reimbursement, the clinicians caring for most patients with addictive disorders tend to be lower paid nonprofessionals. Although the level of complexity of these patients is generally quite high, with multiple drug problems and multiple coexisting psychiatric disorders, the primary therapists have relatively little training to deal with this complexity. Even when physicians are consulted, they often have little training in the psychopharmacology of addiction because this subject is poorly covered in most residency and medical school curricula. Thus, there is a tendency to underutilize the available psychopharmacological tools for improving the treatment of addictive disorders.

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