ARTICLES

Pharmacologic Treatments for Heroin and Cocaine Dependence

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Given the difficulty of achieving sustained recovery, pharmacotherapy of opioid and cocaine addiction is more effective when combined with behavioral and psychosocial approaches. Effective pharmacotherapies for opioid dependence and withdrawal include methadone, L-alpha acetylmethadol (LAAM), naltrexone, buprenorphine, and clonidine. Treatment of cocaine addiction includes anti-craving agents, dopamine agonists or blocking agents, antidepressants, and treatment of co-morbid psychiatric disorders, but all with mixed results. In this paper, we discuss the use of medication in the context of general principles of opioid and cocaine addiction treatment. Both established medications and promising directions in pharmacotherapy will be addressed. (Am J Addict 2003; 12[Suppl 2]:S5-S18)

The descent to Hell is easy;
The gates stand open day and night;
But to reclimb the slope,
And escape to the upper air,
This is labor.
—Virgil, The Aeneid, Book VI, Line 126

Received November 11, 2002; accepted February 14, 2003.
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As the above quote points out, it’s easy to become addicted: the “gates of hell” stand open day and night. But climbing back up—recovery—is very hard. This paper will cover pharmacological treatments for opiate and cocaine addiction, including both established medications and promising directions—treatments that may be helpful to those who endeavor to reclimb the slope. First, however, there are some general treatment principles that apply regardless of the addiction or medication (see Table 1).

Treatment works—just not as often or as well as we would like. The caveat is necessary to temper the promise implied in the “Treatment Works” slogan, which invariably is disbelieved anyway by policy makers who know how often individuals relapse post-treatment. The corollary is that all treatments appear to work for some individuals, but efficacy rates can vary widely. Also unclear are the distinguishing features of these subgroups: the addicted population is heterogeneous, and it would be surprising if any one treatment did work for all or even for most addicts. Anyone who claims to have “the” best treatment for addiction, whether it’s a medication, behavioral intervention, or twelve-step self-help approach, is lying, or at least exaggerating—to you, him/herself, or both. There is no one best treatment because the addicted population is extremely diverse.

Some addicts need addiction treatment to restore their lives to their previous state. Others need addiction treatment combined with a variety of other approaches because they lack important life skills—vocational, educational, or interpersonal—and need to learn them as a part of treatment or via referral. Likewise, although treating psychiatric problems will not cure the addiction, relapse is much more likely to occur if the concomitant psychiatric disorder is not diagnosed and treated.

**TABLE 1. Kleber’s Ten Principles of Treatment**

1. Treatment works, just not as often or as well as we would like.
2. All treatments work for some individuals. But is it for 5% or 50% of the population, and who are they?
3. No one treatment is effective for all drug abusers. The heterogeneity of the population requires a variety of approaches.
4. Some addicts need rehabilitation; others need habilitation.
5. Treating psychiatric problems will not cure the addiction, but relapse will be more probable if you don’t.
6. Legal coercion into treatment (involuntary treatment) works about as well as voluntary—as long as it’s voluntary.
7. Effects of in-prison treatment will decay unless followed by after-care. Self-help programs can be an important resource both in prison and in the community.
8. In general, longer duration in treatment is associated with better outcome.
9. Work is important for long-term abstinence. Skilled, well-compensated jobs are better than their opposite, but some work is better than no work.
10. Medications can be useful for treating many drug abusers, but they usually need to be combined with behavioral approaches.

Legal coercion or involuntary treatment is about as effective as voluntary treatment, as long as the decision is indeed voluntary. That is, the judge should not mandate treatment but rather offer the choice of treatment or jail. The spouse should not say, “You must go into treatment,” but instead, “If you do not go into treatment, I’ll leave you.” The addicted individual should have a clear
choice of the treatment or the alternative. In that sense, all treatment should be voluntary to be more effective.

Treatment in prison can be effective, but in general only if it is followed by aftercare. No matter how good the prison treatment, the effects will decay markedly unless an outpatient or halfway house program follows it. Self-help programs can be enormously helpful during this post-prison phase and should be started while still incarcerated.

In general, longer duration in treatment is associated with a better outcome as long as the treatment is relevant to the patient’s needs. Instruments such as the Addiction Severity Index can be useful in identifying areas in which help is needed. The idea that longer treatment duration is better, however, flies directly in the face of how most treatment is managed and paid for today.

Work is another important tool for long-term abstinence. Skilled, well-compensated jobs are better than their opposite, but some type of work is better than no work activity at all. It’s very hard to treat people who have extensive free time available on days or weekends: they’re much more likely to get into trouble and relapse.

Finally, although this paper reviews various medications to treat different addictions, they rarely are effective by themselves. These general principles of addiction treatment are intended to underscore that pharmacological approaches need to be combined with behavioral and psychosocial approaches.

### TREATMENT OF OPIOID DEPENDENCE

#### Background

Table 2 describes the relative likelihood of dependence for the major drugs of abuse. Nicotine is the most addictive drug when considering only the proportion of individuals who try it and become addicted. Approximately one of every three persons who have at least one cigarette in their life ends up meeting criteria for DSM-IV Nicotine Dependence. Using the same definition, the next most likely drug to cause addiction is heroin. Approximately one in every four individuals who tries heroin ends up meeting criteria for DSM-IV dependence. Thus, the more available heroin becomes, physically or economically, the greater the number of individuals who will become addicted to it.

The current estimate of the number of heroin addicts in the United States is between 800,000 and one million. Heroin use has risen since the mid-1980s, fueled by increased purity and decreased price. Non-injectable routes such as snorting and smoking, which are easier for the novice to contemplate than intravenous use, become more feasible in these circumstances.

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Proportion of Users that Ever Became Dependent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>32%</td>
</tr>
<tr>
<td>Heroin</td>
<td>23%</td>
</tr>
<tr>
<td>Cocaine</td>
<td>17%–23%</td>
</tr>
<tr>
<td>Alcohol</td>
<td>15%</td>
</tr>
<tr>
<td>Marijuana (including hashish)</td>
<td>9%</td>
</tr>
<tr>
<td>Anxiolytics (including sedatives &amp; hypnotic drugs)</td>
<td>9%</td>
</tr>
</tbody>
</table>

While there are more medications available for treating heroin addiction than cocaine or alcohol addiction, there exists significant controversy about such use. Many individuals, both professionals and lay people, feel it is wrong to treat addiction with “other drugs.” Such thinking sets chemical dependence apart from other chronic diseases, a notion refuted by recent evidence. The work of O’Brien and McLellan has revealed a number of similarities between addiction and other chronic disorders such as diabetes, asthma, and hypertension, including the rates of successful treatment outcomes. In any of the above chronic disorders, no one treatment is effective for all patients. Instead, the right treatment for each patient involves a combination of physiologic and behavioral components. In diabetes, for example, some patients need insulin, some can get along on diet changes, and some need oral hypoglycemics. Just as the insulin-dependent diabetic is not viewed as a lesser person, using medications to treat drug dependence does not mean that such patients are weaker or less moral. Similarly, pharmacotherapy for addiction is not “curative,” with the exception of the treatments for withdrawal or overdose. Withdrawal from heroin use is readily “cured” by medications such as clonidine, and heroin overdose is reversed quickly by an injection of the narcotic antagonist naloxone. (In a minute or so, the patient who was barely breathing is wide awake, alert, and wanting to leave the emergency room.) For that moment the physician has, in effect, “cured” the overdose. That’s about as close as any of today’s medications can come to providing a cure for the problems associated with opiate abuse. Perhaps some day we will learn how to reverse the brain changes associated with addiction that prevent it from being cured in the way that infection is cured by antibiotics. While our understanding of these neurological changes grows ever deeper, we do not yet appear to be close to knowing how to reverse them.

Most of the time, therefore, pharmacotherapy is used to increase the holding power of treatment, creating a window of opportunity during which patients can receive the psychosocial interventions and the relapse prevention training that will help them decrease their risk of relapse. For some, long-term maintenance on an agonist such as methadone or an antagonist such as naltrexone is necessary to continue abstinence from illicit drugs and maintain overall functioning. Again, medications typically are not effective alone, so the pharmacotherapies discussed in this paper are considered valid strategies only if prescribed in the context of psychosocial interventions.

Opiate addiction pharmacotherapy includes agonists, partial agonists, antagonists, anti-withdrawal agents, and, most recently, possible anti-craving agents. In spite of all these agents, however, it is estimated that fewer than 200,000 of the million or so heroin addicts in the United States are receiving any kind of treatment. Clearly the challenges at hand are to enhance and expand outreach to these individuals and to come up with treatments that are more likely to get them involved in recovery and keep them engaged.

**Narcotic Agonists**

The two principal agonists used for opiate dependence are methadone and L-alpha acetylmethadol (LAAM). Methadone maintenance is the best-studied and most effective opiate treatment, but it also is the most controversial. In contrast to heroin, which is relatively ineffective (when taken orally), short acting, and very euphorogenic, methadone is an orally effective, 24-hour opioid with minimal psychoactive effects in the tolerant individual. It can block the effects of usual doses of heroin by cross-tolerance if the
methadone dose is high enough, yet leaves the patient able to work or attend school, free of the craving and drug-seeking behavior of heroin-addicted individuals. Approximately 170,000 individuals are maintained on methadone across the United States, usually for only a few years, though a minority may need to stay on almost indefinitely. When the methadone dose is less than 40mg/day, use of heroin remains high; above 80mg/day, heroin use is sharply lower. Patients often prefer the lower dose, however, so they can continue to use heroin and experience its euphoric effects.

In well-run methadone programs, as demonstrated in the 1993 McLellan et al. study, opiate use (like cocaine use) is decreased, and there is marked improvement in a variety of psychosocial indices. Even needle sharing dropped markedly. In programs that do not offer comprehensive services or provide sanctions for cocaine use, the number of patients with cocaine problems may be as high as 50% or more. As for-profit methadone programs have proliferated, methadone programs with minimal services and lax rules have become pervasive.

Methadone can be a difficult drug from which to withdraw. As the dose is lowered below 25–30mg, the therapeutic effects may not last 24 hours, and the patient may go into withdrawal before the next dose, making it difficult to withdraw totally without adverse side effects. While the vast majority of patients receiving methadone do so in a clinic setting with strict take-home rules, there has been some research done with office-based prescribing for patients who have done well in the clinic. This may become more common as regulations are relaxed.

The long-acting form of methadone, L-alpha acetylmethadol (LAAM), originally offered the promise of improved outcomes because it appeared to be an easier drug from which to withdraw and could last as long as three days, thus requiring fewer clinic visits. Initial enthusiasm for the medication suffered a blow, however, when an increase in Torsade de pointes, a potentially fatal ventricular arrhythmia associated with LAAM and a number of antipsychotics and other medications, was recognized just as LAAM was beginning to catch on. The FDA since has required that a “black box” warning be included on the package insert, ruling that LAAM cannot be used as a first-line therapy for the treatment of opiate addiction. Furthermore, LAAM is more expensive than methadone, and using it would necessitate periodic EKGs. From a practical point of view, therefore, although LAAM could have been a useful addition to our arsenal for treatment of opiate addiction, it appears unlikely that it will have such a role.

Narcotic Antagonists

Methadone is an agonist that satisfies craving by occupying the mu receptor and blocks heroin effects by cross-tolerance. Naltrexone is a narcotic antagonist that blocks the ability of opiates to access the mu receptor by competitive antagonism and has roughly 140 times greater affinity for the mu receptor than morphine does. Naltrexone is orally effective, lasts from 24 to 72 hours depending on the dose, and has minimal side effects. Patients need to be off opiates, however, to begin naltrexone therapy: if naltrexone is administered to someone who currently is addicted to opiates, it precipitates immediate and potentially severe withdrawal. Patients need to be off heroin or other short-acting opioids for approximately one week and off methadone for 10–14 days. Naltrexone can be abruptly stopped without withdrawal, and tolerance to its antagonist effects does not occur even after four or five years on the medication.6

Naltrexone has been described as an “ideal drug” for the treatment of
addiction—with the exception that most addicts are uninterested in using it.\textsuperscript{7} Naltrexone’s strengths as a treatment for narcotic addiction are also its weaknesses: it produces no agonist effects, and there are no withdrawal symptoms following discontinuation. Patients who abruptly discontinue methadone go into narcotic withdrawal—a factor influencing good patient compliance with methadone maintenance schedules. Patients who abruptly discontinue naltrexone, however, do not experience physical withdrawal symptoms. Further, after the antagonist effects of naltrexone decay (3–4 days), the euphoric effects of heroin return upon use.

Therefore, naltrexone has been primarily useful for individuals with external contingencies: physicians at threat of losing their license, other professionals such as lawyers or real estate brokers, and individuals on closely supervised probation—in short, those groups who are motivated to continue naltrexone therapy voluntarily because of the unpleasant contingencies if they relapse back to heroin. In general, nurses or physicians who are addicted to opiates and have access to them probably should not be permitted back on staff unless they are on supervised naltrexone for at least a year. This gives both the patients security that they can be around opiates and not relapse and provides the hospital security as well. The key word is supervised: naltrexone kept in a pocket or “cheeked” doesn’t block the euphoric effect of opiates. Supervision is usually done by a family member or a health professional. Naltrexone was approved by the FDA for the treatment of opioid addiction in 1984 and the treatment of alcoholism in 1994. While retention can be as high as 45% with appropriate therapy, it’s more commonly as low as 15 to 20% at six months.

Typical naltrexone dosages are 50mg daily or 100mg on Monday, 100mg on Wednesday, and 150mg on Friday. A promising new approach explored by Comer and Fischman\textsuperscript{8} at Columbia is depot naltrexone, an injectable formulation that blocks the euphoric effects of heroin for 4–5 weeks. Just as the injectable antipsychotics have improved treatment of schizophrenia by minimizing the problem of compliance, likewise depot naltrexone may improve treatment outcome for opiate addicts in a variety of settings.

One climate that may be ideal for the use of depot naltrexone is the probation system, where naltrexone currently is underutilized. A study at the University of Pennsylvania\textsuperscript{9} found that federal probationers randomly assigned to counseling alone were twice as likely to relapse by the end of six months as those assigned to counseling plus naltrexone, roughly two-thirds versus one-third. Although the results were dramatic, probation officials showed little interest in expanding the study. The criminal justice system, with some exceptions, is resistant to using medications. (One such exception for a procedure rather than a medication is in the treatment of cocaine addiction, where acupuncture is employed routinely despite sparse evidence of efficacy.\textsuperscript{10})

### Partial Agonists

The newest maintenance agent, approved in October 2002 by the FDA, is buprenorphine. Buprenorphine is a high affinity partial mu agonist and kappa antagonist. As a partial mu agonist, it has decreased opioid agonist effects, including less respiratory depression, which decreases the likelihood of fatal overdose. Although killing oneself with buprenorphine is difficult, it is not impossible if combined with a drug that depresses respiration by a different mechanism, such as a benzodiazepine.\textsuperscript{11} The ceiling agonist effect is approximately at 32mg of the sub-lingual tablet.

The withdrawal syndrome from buprenorphine is very mild compared to
methadone or heroin, creating a number of possibilities. It can be used either as a maintenance agent in its own right or to transition a patient from agonist (eg, heroin or methadone) to antagonist (eg, naltrexone). It can be used as a transition agent to a drug-free state when given to an individual dependent on an agonist. If buprenorphine is administered to someone already dependent on opiates, withdrawal can be precipitated if the buprenorphine dose is too high (ie, antagonist effect) or too low (ie, inadequate cross-tolerance). Starting patients on buprenorphine therapy, therefore, is not a simple proposition. Buprenorphine should not be given to the opioid-dependent individual until that person is experiencing withdrawal. This may be difficult to achieve if, for example, the patient comes to the office and wants to leave promptly for work or school. The physician needs to insist that the patient remain in the waiting room until withdrawal occurs or request that the patient return when in withdrawal. If withdrawal is not present upon buprenorphine administration, it is more likely that the drug will precipitate withdrawal.

In addition to assessing the state of drug dependence, the initial evaluation should assess for comorbidity and psychosocial needs and how these will be managed. Under the Federal Drug Treatment Act of 2000, buprenorphine will be available for office-based prescribing since the FDA classified it as a Schedule III Controlled Substance. Two medication forms are now available in pharmacies. One form is a 4:1 combination of buprenorphine and naloxone (eg, buprenorphine 8mg and naloxone 2mg) intended for sublingual administration. The naloxone is included as an abuse deterrent, since the combination is planned to be available outside of methadone clinics as a prescription, increasing its availability in the community.

Naloxone, a short acting opioid antagonist, is poorly absorbed orally; thus, if the combination form is taken as prescribed, there is minimal naloxone absorbed and bio-available, and no narcotic withdrawal symptoms will be precipitated. If, however, the patient decides to inject the buprenorphine/naloxone combination for abuse (since buprenorphine is a partial agonist, euphoric effects will be experienced at high doses), there is almost a 100-fold increase in available naloxone. If the patient is physically dependent on an opiate, the injected naloxone will precipitate immediate and severe withdrawal. The initial hope was that the naloxone would also blunt any euphoric effects of buprenorphine, but recent research suggests that in the individual who is not dependent, injecting the combination form does not block all of the euphoric effects of the buprenorphine.

The other form available is buprenorphine monotherapy, intended for the treatment of pregnant addicts and perhaps for the treatment of withdrawal in non-pregnant addicts. This alternative to the combination form is necessary because naloxone, even sublingual, is not approved for use during pregnancy.

Physicians prescribing buprenorphine for treatment of withdrawal or dependence (but not for pain) will be required to complete eight hours of training. Courses are available on-line or through a variety of groups, including the AMA, APA, AAFP, and AAAP. Physicians who do not have credentials such as board certification in Addiction Psychiatry or ASAM (American Society of Addiction Medicine) certification can become qualified to prescribe buprenorphine by completing one of the eight-hour courses and applying to the Secretary of Health and Human Services for prescribing permission. Those who prescribe buprenorphine will need either to provide necessary psychosocial services or refer the patient to such services. Under law, physicians are limited to 30 patients at any one time.
The ceiling effect of buprenorphine applies not only to respiratory depression but also to the agonist effects. It appears that 24–32mg of sublingual buprenorphine is approximately equal to 65mg of methadone in retention and reducing opiate use. For individuals who are being maintained on high dose methadone, eg, 150 or 200mg, buprenorphine probably would not be an adequate substitute unless they can get down to a lower dose. Most current protocols require that patients receive no higher than 40mg of methadone for transition to buprenorphine.

The effective buprenorphine dose will probably range from 16 to 32mg sublingual; at higher doses, it can be given every other day or even every third day.14 Buprenorphine is inherently long acting. Effects on concurrent cocaine use are unclear. Earlier animal studies suggested that buprenorphine decreased cocaine use, but this has not been confirmed in clinical studies. Anticipated advantages of buprenorphine include lower risk of overdose, easier withdrawal, and the ability to prescribe it in an office setting (and thus reduce the need for clinic visits). The risks of office-based prescribing include possible diversion to the street market and inadequate psychosocial rehabilitation efforts.

**Detoxification**

Detoxification can be the entrance into treatment, but many (particularly outpatients) who begin do not complete the process, and many who do complete do not go on to more definitive treatment.15 One reason is that many addicts who enter detoxification do so only to lower their level of dependence and thus make their habit cheaper. The most common detoxification method is methadone taper. The addict is switched from heroin to methadone and the dose is reduced gradually. Usually this can be accomplished in 5–10 days, but at times detoxification is stretched out over weeks. The method is easy to use and has few side effects, but it requires a special license, the dropout and relapse rates are high, and it makes transition to naltrexone difficult because of the longer wait involved.

Another detoxification method involves the use of clonidine, an alpha 2-adrenergic agonist that relieves 80–85% of withdrawal symptoms. Clonidine is not an opioid and therefore requires no special license. It shortens withdrawal from methadone maintenance, although not from heroin, and unlike methadone withdrawal there is less likelihood of rebound (ie, emergence of mild withdrawal symptoms) after the last dose. Clonidine, however, is more difficult to use than the methadone taper, is more likely to cause sedation, and due to its antihypertensive properties requires blood pressure monitoring. Withdrawal symptoms not relieved by methadone or clonidine are treated with agents such as non-steroidal anti-inflammatory drugs (NSAIDs) or ibuprofen for muscle aches and zolpidem, chloral hydrate, or trazadone for insomnia.16

A third alternative for withdrawal is utilization of one of the rapid detoxification methods. The general principle is the use of a narcotic antagonist to precipitate immediate withdrawal by displacing opiates from the receptor sites. The techniques vary in how rapidly they work, which can depend on the dose of antagonist, the drugs used to ameliorate the precipitated withdrawal symptoms, and whether the patient is awake during the procedure. In the oldest of the rapid detoxification procedures (dating back to the early 1980s), the patient is pre-medicated with clonidine and a benzodiazepine (eg, oxazepam or clonazepam) approximately one hour before low dose naltrexone is begun. Over the next day or two, the dose of naltrexone is increased and withdrawal symptoms are treated symptomatically, and by the third or fourth morning, the patient is on the full 50mg/day dosage.17 The procedure is somewhat...
more difficult and more labor intensive than clonidine alone, especially on day one, and as a result has not become popular.

A second rapid detoxification method takes advantage of the withdrawal pattern of buprenorphine, which is more benign than that of heroin. The patient is switched from heroin to buprenorphine for one day, and no opiate the next day, after which the clonidine/naltrexone procedure is initiated. The procedure is relatively easy with tolerable withdrawal symptoms.

The third rapid detoxification method, ultra rapid detoxification, involves either heavy sedation, such as with midazolam, or general anesthesia. In the latter procedure, the patient is placed under general anesthesia for 4–6 hours with an agent such as propofol, withdrawal is initiated with an antagonist such as naltrexone or nalmefene, and a variety of other medications are administered to decrease withdrawal symptoms. Some symptoms, such as diarrhea, vomiting, and severe muscle aches, can persist for hours, days, or even weeks but can be controlled with various medications such as octreotide, ondansetron, and NSAIDs. The procedure has been associated with a number of deaths, mainly related to pulmonary edema, for which the mechanism is not clear. While pulmonary edema usually is attributed to agonist overdose, pulmonary edema without the presence of agonists has been at least the proximal cause in most of the deaths worldwide from this technique, and it tends to occur not during the procedure but 8–72 hours later.

Given the deaths, the potential morbidity, and the lack of any clear cut outcome data that show ultra rapid detoxification to be more effective than other safer and less expensive methods, the procedure should be considered experimental.18–21 Buprenorphine rapid detoxification appears to be the best method to date, although the field continues to evolve. Regardless of the method employed, however, the psychosocial supports that medical staffs provide are critical to completing detoxification and entering longer-term treatment.

The Next Five Years

A long-acting, injectable depot naltrexone should be on the market in 3–5 years, as well as naltrexone implants, which could last for a year or so. Office-based prescribing for buprenorphine is now permissible, and if successful, there will be an increased push for office-based prescribing of methadone for stabilized patients. The most likely office-based scenario is that buprenorphine prescriptions will be permitted for new patients and methadone only for patients already stabilized and doing well. It needs to be emphasized that buprenorphine, like methadone, is a medication, not a treatment. Use of buprenorphine requires appropriate psychosocial supports, which may be problematic in some circumstances. Finally, safer and more rapid detoxification methods are likely to emerge soon. Lofexidine, a clonidine analog but with fewer side effects, is currently in use in the UK and should become available in the U.S. presently.22 Other exciting areas of innovation include being able to alter protracted craving or alter the brain changes that are associated with chronic opioid use, but these advances likely are at least five to ten years away.

TREATMENT OF COCAINE DEPENDENCE

As noted earlier, heroin is the second most likely drug to engender dependence in those who try it, and cocaine is the third. Snorting powder cocaine (cocaine hydrochloride) leads to about 17% of the individuals who ever try it ending up dependent. With crack, the smoked base form of cocaine, as many as 23% will end up dependent. Assuming an average of the
two yields, approximately one in five who try cocaine end up dependent. The estimate for alcohol is around 15%, and 9% of those who ever try marijuana eventually meet criteria for DSM-IV dependence.1

The medical field has been trying to come up with a satisfactory treatment for cocaine addiction almost as long as the drug has been available in Europe and the United States.23 An 1890 letter in *Lancet*, for example, expresses the frustration of a physician with a patient who suffers from “intractable cocaine use, craving, loss of appetite, great nervousness, and sleeplessness.” More than forty medications have been investigated over the past twenty years as treatments for cocaine dependence, but none has shown adequate effectiveness. The search continues, however, because although there are non-pharmacologic treatment options for cocaine,24-25 many patients do not adequately respond or are unable to maintain abstinence after treatment.

**Anti-craving Agents**

Unlike heroin addiction, cocaine withdrawal produces minimal physical symptoms but substantial psychological ones. These can be described as “physiological withdrawal expressed psychologically,” and they share certain common characteristics with nicotine and marijuana withdrawal. Even though the withdrawal is relatively mild, most patients who stop cocaine will experience craving that may persist for weeks and often leads to relapse.26 Thus, there is a need for anti-craving agents for both short- and long-term use.

The dopaminergic system has been the major focus of the search for anti-craving medications, based on the hypothesis that dopamine receptor dysfunction and possibly related dopamine depletion may be producing the craving.27 Newly abstinent cocaine abusers have decreased dopamine binding at postsynaptic dopamine receptor sites28 and are less likely to release dopamine when challenged with IV methylphenidate,29 suggesting that medications that correct or compensate for these effects might treat craving.

Consistent with this hypothesis, medications that affect the dopamine system, including bromocriptine, pergolide, amantadine, mazindol, methylphenidate, and dextroamphetamine, have been tested with varying success.12 Furthermore, open trials have not been confirmed by double-blind ones, early trials have not been confirmed by subsequent ones, and results from trial to trial have been contradictory. This situation suggests that if there is an effect, it is not a robust one, or that any possible medication effect is obscured by the abundant heterogeneity in the sample population.

A recent approach uses disulfiram to increase dopamine levels indirectly. Disulfiram traditionally has been used to treat alcoholism because of the aversive effects experienced when the two are combined. However, it also acts centrally by inhibiting β-hydroxylase, thereby increasing dopamine and decreasing the synthesis of norepinephrine. In double-blind, placebo-controlled trials, disulfiram reduced cocaine use in cocaine abusers with alcohol abuse or dependence and among methadone-maintained cocaine abusers without alcohol dependence or abuse. Replication and extension to non-codependent populations are needed.30-32

Many medications that have been tested for treatment of cocaine dependence initially were developed to treat depression. Chronic cocaine users may suffer from the same underlying catecholamine or serotonergic derangements as those with depression. The tricyclic antidepressant desipramine (DMI) has been the most widely studied, but results have included both positive and negative double-blind trials.33-34 A clue as to the cause of the
disparate results may be in the findings by Fischman et al.\textsuperscript{35} in their human laboratory studies using desipramine with cocaine abusers. They found that although DMI-treated subjects reported fewer positive and more negative effects from cocaine use, self-administration of cocaine continued. This suggests that for individuals with something major to lose by continued cocaine use (e.g., physicians, business executives, lawyers, or those with good psychosocial support networks), the diminished effects that result from combining DMI and cocaine may provide a sufficient decrease in the reinforcement of drug-seeking behavior to help them stop. For those patients with little to lose (e.g., those lacking adequate vocational, educational, or interpersonal skills and who see little future), however, a diminished cocaine effect may be better than no cocaine effect, thus providing insufficient motivation to stop their cocaine use. Newer antidepressants that act via other mechanisms (e.g., fluoxetine and bupropion) have also been investigated, but results have been no better. Unfortunately, neither have results from double-blind trials for other types of medications, such as carbamazepine and buprenorphine. At this time, it does not appear that antidepressants provide useful cocaine addiction treatment agents,\textsuperscript{12} with the exception of those patients comorbid with cocaine dependence and depression.

### Blocking Agents

Another pharmacologic approach to treating addiction is via agents that might block the euphoric effects of cocaine. The main targets of this approach have been the dopamine receptors. Neither flupenthixol decanoate nor risperidone, a newer atypical antipsychotic, has been effective in double-blind trials with non-psychotic cocaine abusers. In a human laboratory study, ecopipam, a dopamine D\textsubscript{1} and D\textsubscript{5} antagonist, was associated with an increase in smoked cocaine, and users had increased subjective effects compared to those on placebo. To date and with limited studies, antagonists have shown minimal results\textsuperscript{12} as potential cocaine abuse treatments.

### Psychiatric Comorbidity

There is a high percentage of psychiatric comorbidity among cocaine abusers. In the absence of a generally effective medication, researchers have looked at heterogeneous specific psychiatric subpopulations that might respond to treatment of psychiatric symptoms. If the psychiatric symptoms are treated properly, patients might be better able to use behavioral strategies to reduce their drug use. Adequately controlled studies involving comorbid cocaine patients are lacking, but there are a number of promising treatment leads. The main comorbid disorders studied have been depression, ADHD, and schizophrenia. The literature for depressed cocaine abusers is not robust. Using secondary analyses, it was found that bupropion\textsuperscript{36} and desipramine\textsuperscript{37} reduced both depressive symptoms and cocaine use in cocaine-abusing, methadone-maintained patients with comorbid depression but not in cocaine abusers without comorbid depression. In a double-blind study among methadone-maintained cocaine-abusing patients,\textsuperscript{38} imipramine reduced depressive symptoms and self-reported cocaine use compared to placebo but not cocaine use measured by urine toxicology testing.

In a study of non-opiate-dependent, depressed cocaine abusers, desipramine patients had fewer depressive symptoms than those on placebo but no significant reduction in cocaine use.\textsuperscript{39} Attention-deficit hyperactivity disorder (ADHD) also has been recognized increasingly in substance abusers and particularly in cocaine abusers. Double blind, placebo-controlled trials of
Stimulants or antidepressants in this population are ongoing based on promising results in case reports and open trials. Schizophrenic cocaine abusers may respond as well as non-substance-abusing schizophrenic patients have to clozapine, olanzapine, or flupenthixol decanoate, but no controlled trials are available. Another approach is to add abuse therapy medications while maintaining schizophrenic patients on their currently prescribed neuroleptic. In open trials, desipramine or selegiline added to antipsychotic medication reduced cocaine use, increased abstinence rates, and improved treatment. In a randomized, double-blind trial, desipramine was more likely than placebo to reduce cocaine use during active treatment and for almost two months following discontinuation of desipramine.40

The Next Ten Years12

Agonists such as GBR 12909 and its long-acting derivatives and PTT, a cocaine analog, may be promising therapies for opiate addiction. These compounds bind to the dopamine transporter with much higher affinity than cocaine, thereby preventing its acute, euphoric effects.

Biochemical approaches aimed at preventing or slowing the cocaine molecule from entering the brain and exerting euphoric effects are being studied, including an immunologic approach analogous to the use of vaccines. By attaching several cocaine fragments to a larger protein molecule, an immune reaction to cocaine in the bloodstream can be stimulated. A form of this vaccine currently is being studied in Phase II human trials.

Another therapeutic model involves stimulating the activity of butyrylcholine-esterase (BChE), a liver enzyme that can break down cocaine in the periphery. Boosting BChE may prove more useful for the acute treatment of cocaine overdose than for relapse prevention. One interesting model that combines enzymatic and immune approaches involves the administration of catalytic antibodies, a novel class of artificial enzymes that can bind to the cocaine molecule in the bloodstream and break it down. The use of catalytic antibody therapies may prove to be beneficial in the treatment of overdose and as relapse prevention.

Other proposed strategies involve blocking the cocaine binding site on the dopamine transporter, blocking postsynaptic dopamine receptors, or stimulating dopamine receptors with agonists and partial agonists. Blocking the pharmacologic effects of cocaine has not been successful with patients. An alternate approach would involve interventions directed primarily at reactivity to factors that elicit drug seeking and drug taking. Exposure to stress, small doses of the stimulant, or environmental cues all can elicit craving for the drug and lead to relapse, a high risk of which persists for a long time after termination of drug use.

Glutamatergic antagonists block many of the behavioral effects induced by chronic administration of cocaine and acquisition of cocaine self-administration in animals. Clinically available medications, such as memantine and dextromethorphan, are capable of inhibiting cocaine self-administration. Other glutamate-related medications under investigation include lamotrigine, baclofen, and gabapentin.

CONCLUSION

Some success in the treatment of opioid and cocaine dependence has been seen, although much improvement is necessary to provide effective treatment for the large numbers of individuals with addiction problems and their tendency to relapse even after successful treatment. While medications by themselves are unlikely to provide adequate solutions for these
problems, they could significantly improve outcomes in combination with existing behavioral methods. A number of useful medications already exist for treating opioid dependence, and the next decade should witness the emergence of more effective ones for the treatment of both opioid and cocaine dependence.

REFERENCES


