Overview of Potential Treatment Medications for Cocaine Dependence

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INTRODUCTION

The search for a pharmacotherapeutic agent for the treatment of cocaine dependence began in the early 1980s as clinicians and researchers realized that the cocaine epidemic was growing rapidly and that standard drug counseling and self-help groups made little impact on the addiction for many cocaine abusers. Cocaine was initially viewed as a recreational drug for the wealthy with limited negative consequences for the majority of users (Grinspoon and Bakalar 1980). The widespread availability of cocaine and increased prevalence of more addictive routes of administration (intravenous (IV) and smoked) have resulted in cocaine abuse and dependence becoming one of the most serious public health problems in the United States. The National Institute on Drug Abuse (NIDA) estimates that at least 2 million persons are cocaine abusers and that 1 to 3 million persons are in need of treatment (Kozel and Adams 1985).

Cocaine dependence is different from other major mental and substance use disorders in that intensive research efforts have only been underway for about 15 years. Truly elegant work has provided at least a partial explanation for cocaine-induced behavioral and physiological effects, and epidemiological and treatment research to date has elucidated many of the clinical challenges yet to be met. The lag between an understanding of molecular, cellular, and neurobiological effects of cocaine and their relationship to behavioral responses induced by cocaine has resulted in the testing of pharmacological agents aimed at impacting cocaine abuse based on rationales limited by the scientific and clinical understanding of the disease at that time. The evolution of clinical trials methodologies that will yield more useful clinical information and effectively test underlying hypotheses continues. The gaps in scientists' knowledge and limits in clinical methodology to date have restricted the clinical application of many studies. Given these limitations, it is not surprising that no widely efficacious pharmacotherapy for the treatment of cocaine dependence has emerged thus far.

This chapter will summarize the most recent efforts to identify an effective medication for the treatment of cocaine dependence with a focus on work reported over the last 5 years. Some of the clinical attributes for development of an ideal pharmacotherapy will be discussed, as well as rationales utilized for selecting potential pharmacotherapies. New possibilities for medication treatment of cocaine dependence will be briefly reviewed. These may constitute the rudiments of hypotheses and rationales for effective treatments in the future for this most difficult and challenging disorder.

RATIONALE FOR PHARMACOTHERAPY OF COCAINE DEPENDENCE

Pharmacotherapy of any substance use disorder should be undertaken to address specific problems arising in the course of treatment. For example, the use of medication is often necessary to treat withdrawal syndromes, particularly those in which patients are physiologically addicted to the substance. The choice of a pharmacotherapy for withdrawal should be based on a medical assessment that considers the patient's past and present medical history, as well as consideration of the past history of detoxification and the level(s) of care available. Medication is also considered as a means of relieving craving, especially early in abstinence when such urges put the patient at significant risk for relapse. Effective anticraving medications for most substances of abuse are not available at this time, with the one major exception of methadone maintenance for opiate dependence. Medication treatment may be considered for the initiation and maintenance of abstinence from the substance of abuse. There are limited examples of such medications for the treatment of addictive diseases at this time, including methadone and other long- acting opiates such as buprenorphine or l-alpha-acetylmethadyl (LAAM), which induce tolerance to the effects of opiates. Naltrexone is useful for the treatment of opiate dependence by preventing euphoria when opiates are self-administered. Disulfiram (Antabuse), a drug that results in an aversive physical reaction when alcohol is taken, is a useful adjunct in the treatment of alcohol dependence for selected patients.

Cocaine does not cause physiological dependence, but the psychological addiction in patients with cocaine use disorders can be disabling (Gawin and Ellinwood 1988, 1989). An abstinence syndrome has been described for cocaine dependence and consists of three phases: the "crash," withdrawal, and extinction (Gawin and

Kleber 1986, 1988). Medication management of these phases could be useful for the treatment of cocaine use disorders.

The "crash" is associated with exhaustion following a binge, but other symptoms may occur including agitation, anxiety, depression, and psychosis. These symptoms may require emergent medical and psychiatric evaluation and treatment. An important part of the management of patients with such symptoms is a thorough psychiatric evaluation. Patients in whom symptoms of agitation, psychosis, or depression do not abate over the first few days of treatment, or those in whom such symptoms worsen, may have a comorbid psychiatric disorder that requires psychiatric care. This distinction is critically important in cocaine abusers. Several investigators have shown that comorbid psychiatric disorders occur at high frequency in cocaine abusers (Rounsaville et al. 1991; Weiss and Mirin 1986; Weiss et al. 1988). Further, the lack of appropriate psychiatric care will have a significant negative impact on the patient's ability to initiate and maintain abstinence. Finally, these patients have needs that are not adequately addressed in standard cocaine abuse treatment, which decreases the likelihood that treatment outcome in these patients will be positive. Such individuals require dual diagnosis treatment, which can address both the cocaine abuse and the psychiatric disorder (Hellerstein and Meehan 1987; Martino et al. 1995; Roberts et al. 1992).

The cocaine withdrawal syndrome is a constellation of affective and psychological symptoms lasting from 2 to 10 weeks and is marked by decreased energy, lack of interest, and anhedonia. These symptoms fluctuate and are not severe enough to meet diagnostic criteria for an affective disorder. Symptoms do not occur uniformly in newly abstinent cocaine abusers and, in particular, patients who are hospitalized following cessation of cocaine use may not experience substantial withdrawal symptoms (Brower et al. 1988; Weddington et al. 1990). The cocaine withdrawal syndrome does not generally require medical treatment or pharmacotherapy. However, it is during this time that relapse risk is greatest, so that development of a pharmacotherapy that could assist the patient in initiating and maintaining abstinence would be of great utility in the treatment of cocaine dependence.

DEVELOPMENT OF A PHARMACOTHERAPY FOR COCAINE DEPENDENCE

In developing an effective pharmacotherapy for substance dependence, the various actions of the drug must be identified. Those effects that will decrease substance abuse should be targeted for pharmacotherapy development. In the case of cocaine, there are several effects that may be points for pharmacotherapy intervention. Cocaine dependence is characterized by either daily or binge use of the drug, perpetuated by intense craving that use of the drug induces (Jaffe et al. 1989). An agent that decreases cocaine craving would be useful for treatment of cocaine dependence. Craving is stimulated by the euphoria induced by the drug (the cocaine "high"). A drug that also could diminish cocaine "high" might assist patients in maintaining sobriety. Finally, repeated use of cocaine is associated with dysphoria, paranoia, and agitation. Development of a medication treatment that could accentuate these adverse psychological effects after a single use might also dissuade the cocaine abuser from using subsequent doses of cocaine.

The development of a medication for treatment of cocaine dependence should include consideration of what the "ideal" properties of such a pharmacotherapeutic agent might be. These attributes are summarized in table 1. A medication should be available by a convenient route of administration. Oral preparations are most frequently used and are accepted by patients and clinicians. A preparation that provides for a long-acting medication treatment, such as an intramuscular (depot) formulation, or a transdermal preparation, would offer certain advantages, including a decrease in medication noncompliance and less frequent medication doses. While frequent clinic visits are desirable early in treatment when it is important to engage the patient and assist in the induction of abstinence, frequent visits are less important in later stages of treatment when the patient has been able to utilize treatment effectively and could, in some cases, impede the patient's ability to engage in employment and other activities important to the recovery process.

Medications must be medically safe and have few side effects. Patients must be willing to accept the medication as an important and useful part of treatment for their cocaine dependence. It is important to match patients to treatments. There will be patients who will embrace philosophies of drug abuse treatment that discourage the use of

TABLE 1. *Properties of an ideal pharmacotherapy for cocaine dependence*.

- Convenient route of administration: oral, intramuscular (depot formulation), or transdermal.
- Long acting.
- Medically safe with few side effects.
- Acceptable to patients presenting for treatment.
- Ideally, little abuse liability.
- Useful for more than one class of drug since many cocaine abusers are polysubstance abusers.
- Used in conjunction with behavioral treatments that target the drug abuse and psychosocial problems related to the drug abuse.

medication treatments and rely on group support and internal motivation (such as self-help organizations). Other patients may have comorbid psychiatric disorders that would be more appropriately treated with standard psychotropic medications indicated for the psychiatric disorder. Some patients will have medical disorders that would make them poor candidates for a medication treatment of their drug abuse (e.g., disulfiram would be contraindicated in the alcoholic patient with esophageal varices, and caution must be used in naltrexone treatment of an opiate-dependent individual with hepatic impairment). Finally, stage of treatment for the cocaine addiction must be considered. Pharmacotherapies will be most useful in the withdrawal phase when relapse risk is greatest. It would be unusual to initiate medication for cocaine dependence after several months of sustained abstinence.

An ideal medication treatment for cocaine dependence would have little abuse liability and would be useful for treatment of other addictions in addition to cocaine. Cocaine abusers are often polysubstance abusers and frequently require treatment for alcoholism or opiate abuse/dependence. Marijuana is also a frequently abused drug. At this time, no drug has been shown to be efficacious for treatment of polysubstance abuse, though some promising results have been shown for naltrexone for opiates (Fraser 1990; Ling and Wesson 1990), alcohol (O'Malley et al. 1992; Volpicelli et al. 1992), and disulfiram (for cocaine and alcohol) (Carroll et al. 1993; Van Etten et al. 1994). Finally, any medication treatment must

be utilized in conjunction with psychosocial therapies to maximize clinical benefit to the cocaine-dependent patient.

Pharmacotherapy Approaches

Medications development for cocaine dependence has followed two basic approaches. The first has been an attempt to identify drugs that function as cocaine antagonists, and the second has been to develop drugs with properties similar to cocaine but with a longer duration of action, e.g., cocaine analogs. Cocaine antagonists include drugs that attenuate the acute reinforcement and other effects that have become associated with cocaine use. Advantages to the use of cocaine antagonists are that decreasing euphoric effects of cocaine may be helpful in terminating the abuse of the drug and in enhancing compliance with treatment. Another advantage would be the low abuse liability of these drugs. A problem with the use of cocaine antagonists is that such drugs might produce dysphoria in patients, since the hedonic (and reinforcing) effects of cocaine are thought to be mediated through dopaminergic systems (Fibiger et al. 1992; Koob 1992). Drugs that block the hedonic effects of cocaine could block hedonic effects in general, resulting in dysphoria. Cocaine analogs include drugs that would indirectly block acute cocaine effects by inducing cross-tolerance. Advantages of such drugs include a reduction in cocaine abstinence or withdrawal symptoms and enhanced compliance due to the mood-enhancing effects of the drug. This might assist the patient in breaking the cycle of cocaine use and could be helpful in the treatment engagement process. A problem with this approach could be that cocaine analogs would be stimulant drugs with abuse liability and street value. Stimulant drugs may increase craving for cocaine or possibly increase cocaine use. The use of such drugs would require careful monitoring in an outpatient setting.

PHARMACOTHERAPY FOR COCAINE DEPENDENCE—RECENT RESEARCH

The epidemic of cocaine abuse has resulted in intensive efforts to develop effective treatments. These efforts include development of both psychosocial interventions and medication treatments for cocaine dependence. The purpose of this chapter is to review developments in the search for an effective pharmacotherapy for cocaine dependence. This chapter will also briefly consider additional agents that have yet to be examined, but serve as examples of approaches that represent the rationale of the use of cocaine agonists (medications that share some pharmacological properties of cocaine) and the use of cocaine antagonists

(drugs that, based on pharmacological properties, might antagonize cocaine effects) for the treatment of cocaine addiction.

A large number of medications have been used for treatment of cocaine dependence (table 2). These medications have been utilized for a variety of cocaine-related effects, including treatment of cocaine withdrawal, treatment for cocaine craving, and initiation and maintenance of abstinence. Many of these medications have appeared to be promising in open trials. However, once studied in randomized, placebo-controlled clinical trials, no medications to date have been shown to have substantial efficacy for the treatment of cocaine dependence.

In addition to the lack of strong evidence for efficacy, there have been numerous problems in the interpretation of results from many studies. These difficulties are summarized in table 3. Studies to date have often included small sample sizes and have been hampered by large dropout rates. Diagnostic criteria have varied across clinical trials (some studies enroll patients meeting diagnostic criteria for cocaine dependence, others cocaine abuse, and others do not specify patient diagnosis). It is difficult to know whether the results of a study are generalizable to the population of treatment-seeking, cocaine-addicted individuals. Many of the larger studies have looked at pharmacotherapies for cocaine dependence in patients with primary opiate dependence and who receive methadone maintenance. While this population tends to be more available for followup because of the need to report to a clinic daily for methadone treatment, it is likely that these patients are different from patients with primary cocaine use disorders. Therefore, results obtained in studies enrolling methadone-maintained cocaine abusers may not be generalizable, though certainly such studies are important given the prevalence of cocaine abuse in this group. Outcome variables differ among clinical trials making it difficult to determine a drug's effectiveness. Studies that have utilized self-reports without confirmation by urine toxicology screen may not be reflective of cocaine use by study participants.

Future studies should be double blind and placebo controlled, and include large, diagnostically well-defined samples. Standardized outcome variables to assess the efficacy of the medication treatment

TABLE 2. *Medications t*

Dopaminergic agents

bromocriptine
L-dopa
methylphenidate
mazindol
pergolide
amantadine
flupenthixol
haloperidol
bupropion
selegiline
AMPT
benztropine
ritanserin

Antidepressants

desipramine (DMI)
fluoxetine
sertraline
imipramine
maprotilene
phenelzine
trazodone
lithium

Miscellaneous agents

buprenorphine
carbamazepine
nimodipine
mazindol
nifedipine
disulfiram
clozapine
tyrosine
naltrexone
gepirone
tryptophan
placebo

should be utilized. Regular urine toxicology confirmation of drug use needs to be included in all efficacy trials.

The following sections will summarize recently (primarily the last 3 years, but in some instances up to 5 years) reported studies of pharmacotherapies for cocaine dependence. The summary will include only studies that have been conducted in humans with primary cocaine use disorders (i.e., cocaine abuse or cocaine dependence). Although many studies have been conducted in methadone-maintained, cocaine-abusing patients (i.e., patients with primary opiate dependence), these patients are sufficiently different from primary cocaine-abusing patients both in terms of the neurobiological and physiological effects of the primary drug of abuse and in

terms of the clinical treatment that results reported for them may not be generalizable to those with primary

TABLE 3. *Difficulties wi*

•Outcome variables differ:

Cocaine self-reports.

Urine toxicology screens.

Retention in treatment.

Craving assessments.

Length of abstinence.

Depression.

Cocaine withdrawal symptoms.

•Open-label studies.

•Small sample size.

•High dropout rate.

•Diagnosis at entry: Cocaine abuse versus cocaine dependence.

•Severity of cocaine use is usually not considered.

•Many studies report on opiate-dependent cocaine abusers.

cocaine use disorders. Summaries of the results of preclinical studies will be limited to one very recent report that may have important implications for chronic treatment of humans with the specified agent (haloperidol) and recent preclinical reports that may lead the field in new directions for medication development for cocaine dependence. Finally, the studies reported will include both outpatient clinical trials and inpatient studies that examine the effects of a particular agent on cocaine responses in human volunteers.

Desipramine

Desipramine (DMI), a tricyclic antidepressant agent, was one of the first medications to be studied as a treatment for cocaine dependence and, as such, is one of the most extensively studied pharmacotherapies for

cocaine dependence to date. DMI may act as a specific antianhedonic agent in cocaine-dependent patients (Gawin and Kleber 1986). Several recent controlled clinical trials in cocaine abusers have been reported and are summarized (table 4). One double-blind, placebo-controlled, randomized trial included 29 subjects. In this trial, 14 subjects were randomized to treatment with 40 mg of DMI daily. Outcome variables included cocaine use self-reports, urine toxicology screens, and cocaine craving measures. No significant difference was observed between DMI and placebo treatment in this study (Covi et al. 1993, 1994). A large clinical trial that examined the efficacy of DMI and psychotherapy, alone and in combination, as a treatment for ambulatory cocaine abusers has been reported (Carroll et al. 1994). In this 12-week, double-blind, placebo-controlled trial, 139 subjects were assigned to one of four conditions. These conditions included relapse prevention therapy plus DMI, clinical management plus DMI, relapse prevention plus placebo, and clinical management plus placebo. The mean dose of DMI was 200 mg daily and was adjusted by a nonblinded psychiatrist in response to plasma concentration (target ranges 300 to 750 ng/mL) and side effects. All groups showed significant improvement in treatment retention and a reduction in cocaine use at 12 weeks, but there were no significant main effects for psychotherapy, pharmacotherapy, or the combination. Lower severity patients (cocaine use 1 to 2.5 g/week) had improved abstinence initiation when treated with DMI. DMI was significantly more effective than placebo in reducing cocaine use during the first 6 weeks of treatment. Depressed subjects had a greater reduction in cocaine use than nondepressed subjects and had a better response to relapse prevention therapy. The findings of this study underscore the heterogeneity among cocaine abusers and the need to develop specialized treatments for distinct subgroups of cocaine abusers.

Dopaminergic Agents

The most widely accepted explanation of cocaine-induced euphoria is that dopamine (DA) reuptake inhibition results in increased extracellular DA concentration in the mesolimbic and mesocortical reward pathways in the brain. Numerous studies have provided evidence for the importance of DA in the reinforcing properties of cocaine. Low doses of DA

TABLE 4. *Desipramine (*

Desipramine (DMI)

Rationale: Blocks reuptake of norepinephrine and to a lesser extent dopamine; postulated to act as a specific antianhedonic agent in cocaine-dependent patients.

Controlled studies:

•(Covi et al. 1993, 1994): DMI was not significantly better than placebo.

•(Carroll et al. 1994): DMI may be useful for selected patients: Lower severity patients (cocaine use: 1 to 2.5 g/wk) had significantly longer periods of abstinence.

DMI was associated with improved abstinence initiation weeks 2 through 6 only.

receptor antagonists, when injected systemically, consistently increase cocaine self-administration in animals, indicating a of blockade of cocaine effects (Koob 1992). In addition, 6-hydroxydopamine (6-OHDA) lesions of dopaminergic terminals in the nucleus accumbens produce extinction-like responding and a reduction in cocaine self-administration (Lyness et al. 1979; Roberts et al. 1977, 1980). Similar lesions in other areas of the brain (frontal cortex and caudate nucleus) do not alter cocaine self-administration (Koob et al. 1987; Martin-Iverson et al. 1986). In vivo brain microdialysis has also provided additional experimental data that indicate that mesolimbic DA levels are associated with cocaine reward (Fibiger et al. 1992). Conversely, cocaine abstinence that is characterized by depression, irritability, and anxiety (the "crash") has been hypothesized to result from dopaminergic hypoactivity (Dackis and Gold 1985). Support for this hypothesis is derived from studies of in vivo microdialysis during cocaine withdrawal (Weiss et al. 1992). These experimental findings support the rationale for use of dopaminergic agents in the treatment of cocaine dependence described below.

Dopamine Antagonists

DA antagonists, of which two have been examined (haloperidol and flupenthixol), have been postulated to have potential as treatment agents

for cocaine dependence. This is due to their ability to block specific DA receptors that might alter cocaine acute effects thought to be mediated by a rapid increase in DA in the nucleus accumbens. The effects of haloperidol on subjective and physiologic responses to cocaine was examined in five cocaine-abusing volunteers (Sherer et al. 1989). In a randomized, double-blind study design each subject received either haloperidol 8 mg or placebo followed 20 minutes later by IV cocaine (40 mg) administration. Haloperidol attenuated expected increases in blood pressure, but not heart rate. Haloperidol reduced subject ratings of pleasant sensation following cocaine administration, but had no effect on cocaine euphoria as measured by the variable "rush" (table 5). Flupenthixol is a thioxanthene with DA antagonist properties. It is being examined in controlled, outpatient trials for efficacy in the treatment of cocaine dependence. In a 6-week, double-blind, placebo-controlled study comparing DMI and flupenthixol, an interim data analysis showed a trend toward better engagement in treatment for patients randomized to flupenthixol treatment (Gawin et al. 1993; Khalsa et al. 1994) (table 5).

TABLE 5. *Dopamine (DA) antagonists.*

Rationale: Cocaine euphoria appears to be mediated by a rapid increase in DA in nucleus accumbens; blockade of specific DA receptors may change acute cocaine effects.

Haloperidol

•(Sherer et al. 1989): Pretreatment with haloperidol 8 mg followed by IV cocaine (40 mg) showed decrease in pleasant effects of cocaine, but no effect on cocaine euphoria as measured by "rush."

•(Kosten et al. 1994): Chronic haloperidol treatment enhanced cocaine-induced conditioned place preference (CPP), while acute treatment blocks CPP.

Flupenthixol

•**(**Gawin et al. 1993; Khalsa et al. 1994): A 6-week, double-blind, placebo-controlled study comparing DMI and flupenthixol in cocaine-dependent outpatients showed a trend toward better engagement in treatment in group assigned to flupenthixol.

The effect of both acute and chronic haloperidol treatment on cocaine-conditioned place preference in rats has been recently studied (Kosten et al. 1994). Using a full cocaine dose-response function, acute haloperidol

was shown to block cocaine-conditioned place preference. In contrast, chronic haloperidol treatment resulted in behavioral supersensitivity, lowering the dose of cocaine that supports conditioned place preference. This finding supports those of other studies that show that chronic haloperidol treatment leads to receptor supersensitivity and enhanced locomotor responses to cocaine (LeDuc and Mittleman 1993). This study indicated that haloperidol and similar DA antagonists might be contraindicated for long-term treatment of cocaine abuse. It appears that one possibility is that such agents could contribute to enhanced cocaine effects. These findings may also help to partially explain the high prevalence of cocaine abuse in neuroleptic-maintained schizophrenics (Schneier and Siris 1987).

Dopamine Agonists

It has been postulated that chronic cocaine use may deplete central DA, which could result in supersensitivity of dopaminergic receptors. DA hypofunction induced by cocaine abuse may underlie craving and withdrawal symptoms often observed in recently abstinent cocaine-dependent patients. The following section includes a review of recent studies that have used agents with DA agonist properties in the treatment of cocaine use disorders.

Bromocriptine is an agonist with high affinity for the D_2 receptor. Treatment with bromocriptine might reverse dopaminergic deficits induced by cocaine and ameliorate craving and withdrawal. Two studies have addressed the utility of bromocriptine in the treatment of cocaine dependence by examining effects of pretreatment with bromocriptine on cocaine administration (table 6). Pretreatment with either bromocriptine 2.5 mg or 5 mg 2 hours prior to cocaine administration had no effect on cocaine euphoria; however, heart rate following bromocriptine pretreatment was augmented (Kumor et al. 1989). Another study examined the effects of bromocriptine pretreatment (0, 1.2, or 2.5 mg) on IV cocaine (0, 12.5, 25, or 50 mg) administration. While bromocriptine did not alter the subjective effects of cocaine, significant increases in heart rate were again observed with the combination (Preston et al. 1992).

Controlled outpatient clinical trials have been limited with bromocriptine. Early open studies using doses of 1.25 mg to 2.5 mg daily have yielded

TABLE 6. *Dopamine (DA) agonists.*

Rationale: Cocaine may deplete central DA, which may result in DA receptor supersensitivity and DA hypofunction, which may underlie craving, withdrawal.

Bromocriptine (D_2 agonist)

•(Sherer et al. 1989): Bromocriptine pretreatment (2.5 mg or 5 mg) 2 hours prior to cocaine administration; no effect on cocaine euphoria, increase in heart rate.

•(Preston et al. 1992): Pretreatment with bromocriptine (0, 1.2, 2.5 mg) did not alter subjective effects of cocaine (0, 12.5, 25, 50 mg IV); significant increase in heart rate was observed with the combination.

•Few controlled clinical trials.

•Reports of difficulty with adverse event profile (headache, vertigo, syncope).

Amantadine (DA release)

•(Sholar et al. 1994): Acute effects of amantadine (0, 200 mg, or 400 mg) on intranasal (IN) cocaine administration; attenuation of heart rate increases following cocaine administration for both doses of amantadine; the 200 mg dose was associated with decreased cocaine "high," chronic amantadine administration (100 mg twice daily) enhanced euphoric effects of cocaine in male subjects.

•(Weddington et al. 1991): 12-week, single-blind study (N = 54), all treatment groups showed decrease in cocaine use and craving; no evidence for efficacy of amantadine (400 mg/d).

•(Alterman et al. 1992): Amantadine 100 mg twice daily (N = 42) associated with significantly less cocaine-positive urines than placebo-treated patients, though there was no difference in self-report of cocaine or other substance use.

TABLE 6. *Dopamine (DA) agonists (continued).*

Bupropion (inhibits DA uptake)-Bromocriptine (D_2 agonist)

•(Montoya et al. 1994): 8-week open-label trial using combination of bupropion $\leq$ 300 mg/d and bromocriptine $\leq$ 7.5 mg/d; no decrease in cocaine-positive urines.

L-deprenyl (inhibits DA metabolism)

•(Haberny et al. 1994): Five subjects with history of IV cocaine abuse, 2-day pretreatment with L-deprenyl 10 mg or placebo followed by cocaine (0, 20, 40 mg IV); no alteration of physiological or subjective effects of cocaine by L-deprenyl.

Methylphenidate (DA release)

•(Grabowski et al. 1994): Methylphenidate 20 mg SR twice daily + 5 mg standard versus placebo (N = 7) for 8 weeks; decreased craving in methylphenidate group, no decrease in cocaine use.

conflicting results and suffered from high dropout rates (Dackis et al. 1987; Giannini and Baumgartel 1987). In a double-blind clinical trial using bromocriptine 5 mg to 7.5 mg daily, the study drug was poorly tolerated with frequently reported side effects of headaches, vertigo, and/or syncope resulting in high dropout rates (Tennant and Sagherian 1987). The use of bromocriptine to treat acute cocaine abstinence has recently been revisited in a small, double-blind, placebo-controlled trial (Moscovitz et al. 1993). Bromocriptine 1.25 mg three times daily or placebo was given to patients presenting to an emergency room for minor medical complaints, but who were found to be abusing cocaine by urine toxicology screen. Subjects were given followup appointments four times over a 15-day period. Although the small sample size lacked statistical power to make inference, the investigators found that bromocriptine was generally well tolerated. Five of 14 subjects randomized to bromocriptine returned for all visits and three of these subjects had negative urine toxicology screens on all visits. Subjects randomized to bromocriptine and placebo showed no difference in retention (bromocriptine group 43 percent, placebo group 31 percent). Those randomized to bromocriptine had more urine toxicology screens negative for cocaine (67 percent) than those randomized to placebo (31 percent). Drawbacks to this study include the small sample size and its atypical quality, since these were not subjects seeking treatment for perceived problems with cocaine use. Additionally, there was no monitoring to determine compliance with the study medication. Novel treatments with bromocriptine are being

explored and could include the use of bromocriptine in combination with other agents. For example, an open-label study of the combination of bromocriptine (œ 7.5 mg daily) and bupropion (œ 300 mg daily) was conducted over an 8-week study period (Montoya et al. 1994*a,* 1994*b*). There was a significant reduction in pre- and posttreatment self-reports of cocaine use ($p < 0.01$), but no significant change in urine toxicology screens (both qualitative and quantitative). This study provides evidence for the safety of this combination, but does not support efficacy for the treatment of cocaine dependence. However, these studies indicate that bromocriptine may have some utility in the treatment of cocaine dependence and should be considered in future, well-controlled studies.

Amantadine increases dopaminergic transmission, but whether the mechanism is DA release, direct effects on DA receptors, or DA reuptake blockade is unclear. There have been few recent controlled studies of amantadine for treatment of cocaine dependence. These are summarized in table 6. One study examined the effects of acute amantadine (200 mg or 400 mg) and chronic amantadine (100 mg twice daily for 4 days) followed by insufflation of cocaine 0.9 mg/kg (Sholar et al. 1994). Acute effects of both amantadine doses on cocaine responses included attenuation of heart rate increases, while the amantadine 200 mg dose was associated with a decrease in cocaine "high." Chronic administration of amantadine 100 mg twice daily was associated with increased "high" in male subjects after cocaine administration as compared to female subjects. A 12-week, single-blind comparison of DMI (200 mg daily), amantadine (400 mg daily), or placebo as adjunctive treatments to counseling for cocaine dependence has been reported (Weddington et al. 1991). All treatment groups demonstrated decreased cocaine use, craving, and psychiatric symptoms, indicating no specific treatment effect of the active medication treatments. The effectiveness of amantadine was evaluated in a double-blind, placebo-controlled trial in which 42 patients in a day treatment program were randomized to amantadine 100 mg twice daily (N = 21) to be taken over 10 days or placebo (N = 21). Urine toxicology screens showed that those who had received amantadine were significantly more likely to be free of cocaine ($p < 0.05$) at the 2-week and 1-month followup visits, though self-reports for the two treatment groups did not differ. This study indicated that amantadine may have some efficacy in early treatment of cocaine dependence (Alterman et al. 1992).

Bupropion is a second-generation antidepressant that enhances dopaminergic transmission, but has little effect on serotonergic neurotransmission. To date, experience with bupropion in clinical trials has been limited. In an open pilot study, six methadone-maintained cocaine abusers participated in an 8-week outpatient study in which they

received bupropion 100 mg three times daily (the usual dose used for treatment of depression). At the 8-week followup, only one of the study participants was still using cocaine. At the 3-month followup, the four patients who achieved abstinence from cocaine during bupropion treatment remained free of cocaine use as indicated by self-report and urine analysis (Margolin et al. 1991). The results of a large multicenter study designed to assess the effectiveness of bupropion for treatment of cocaine addiction in methadone-maintained patients showed little evidence for efficacy in this group (Vocci et al. 1994). Another study explored the use of bupropion in conjunction with bromocriptine treatment in primary cocaine abusers (table 6) (Montoya et al. 1994*a*, 1994*b*). Given its DA agonist properties, this drug should be considered for further clinical trials to assess its efficacy for treatment of primary cocaine dependence.

L-deprenyl is a monoamine oxidase type B inhibitor that specifically inhibits the metabolism of DA. Its present indication is for the treatment of Parkinson's disease. The ability of L-deprenyl to potentiate DA has led to consideration of its use in the treatment of cocaine dependence. A study in five human volunteers examined the effects of L-deprenyl alone and in combination with cocaine (Haberny et al. 1994) (table 6). Subjects were treated with L-deprenyl 10 mg or placebo for 2 days. Each subject participated in cocaine administration sessions following treatment with L-deprenyl and following placebo treatment. Cocaine doses of 0, 20, and 40 mg were administered intravenously at 60-minute intervals. No differences in physiological (cardiovascular) parameters or drug liking were observed for sessions that included cocaine-alone administration or the L-deprenyl-cocaine combination.

Methylphenidate (MP) is a stimulant drug primarily used in the treatment of childhood attention deficit hyperactivity disorder. MP is a DA agonist with pharmacological properties that include DA release and reuptake inhibition. It is being studied as an initial treatment for cocaine dependence (Grabowski et al. 1994) (table 6). This study represents a unique approach to drug development for cocaine dependence. Subjects were cocaine-dependent volunteers who were admitted to an inpatient unit for a 2-day period during which pretreatment safety, physiological, behavioral, and cognitive assessments were made. Subjects were monitored and stabilized for 2 weeks in an outpatient clinic. Subjects (N = 7) were then randomly assigned either to placebo or to MP 20 mg (sustained-release preparation) twice daily and 5 mg of standard MP daily in an 8-week trial. Quantitative urine benzoylecgonine (BE) determinations were conducted on urine samples obtained twice a week and patient self-reports were also elicited. A preliminary report from this

ongoing study has indicated that retention is good, with only one dropout from the MP group thus far. Reported desire to use cocaine and "preoccupation with use" are decreased in the MP group. Nonsignificant increases in blood pressure and pulse were observed in the MP group. No significant difference in abstinence or cocaine use as determined by quantitative urine BE were observed in this small sample. This study demonstrated a novel approach to drug development and showed that this class of medications may be useful in the treatment of cocaine dependence.

Cocaine Antagonists

A variety of medications have been examined for their effectiveness in blocking the reinforcing effects of cocaine. These drugs, including mazindol, fluoxetine, carbamazepine, naltrexone, and disulfiram, which have been the subject of study over the past several years, have a broad range of pharmacological properties, and all differ greatly in primary indication. However, all have been postulated to antagonize the effects of cocaine through pharmacological properties specific to each drug, which might alter neurobiological and reinforcing effects of cocaine.

Mazindol. The euphorigenic and reinforcing effects of cocaine are thought to be related to the effect of cocaine on DA reuptake inhibition. Although the potency of cocaine-like drugs as inhibitors of DA uptake is highly correlated with reinforcement in animal studies, several potent DA uptake blockers do not produce addiction and are not associated with euphoric effects in humans (Rothman 1990). Mazindol is a DA reuptake inhibitor without abuse liability. As such, mazindol may antagonize the effects of cocaine and be useful in the treatment of cocaine dependence. One study has reported on the effects of cocaine alone and in combination with mazindol in cocaine-abusing volunteers (Preston et al. 1993) (table 7). Subjects participated in a crossover study that included 12 acute drug conditions. Subjects were randomized to treatment with mazindol 0, 1, or 2 mg orally 2 hours prior to administration of IV cocaine (0, 12.5, 25, or 50 mg). Cocaine and mazindol alone were found to significantly

Mazindol

Rationale: Blocks DA reuptake, may substitute for cocaine, but with weaker effects, less abuse liability, cocaine use during treatment may be less reinforcing.

•(Stine et al. 1992): Mazindol 2 mg daily or placebo (N = 33); no effect on cocaine use, no significant adverse events.

•(Preston et al. 1993): Mazindol pretreatment (0, 1, and 2 mg) followed by cocaine administration (0, 12.5, 25, 50 mg IV), no evidence that mazindol altered subjective effects of cocaine, but the combination significantly increased heart rate and blood pressure.

Fluoxetine (FLX)

Rationale: A serotonin (5-HT) reuptake inhibitor; cocaine potently inhibits 5-HT reuptake, which may play a role in the dysphoric effects of cocaine; medications such as FLX may accentuate such effects.

•(Walsh et al. 1992): Double-blind placebo crossover study (N = 5), FLX 30 and 40 mg, decreased response to cocaine 40 mg (IV), no correlation between FLX level and cocaine responses.

•(Walsh et al. 1994*a*): Double-blind placebo crossover study (N = 8), dose ranging FLX 0, 20, 40, 60 mg/d, cocaine 0, 20, 40 mg, FLX 40 mg and 60 mg doses decreased subjective effects of cocaine, no cardiovascular toxicity.

•(Batki et al. 1993): Open treatment with FLX (mean dose = 45 mg/d) for 9 weeks in methadone-maintained, cocaine-dependent patients; quantitative urine BE showed significant decrease in amount of cocaine used by the end of the study.

•(Batki et al. 1993): FLX 40 mg versus placebo (N = 32) in cocaine ("crack")-dependent patients. FLX associated with longer retention (11 weeks versus 3 weeks), but there was no difference in quantitative urine BE.

increase heart rate and blood pressure. Mazindol had mild stimulant effects and cocaine increased ratings for stimulant effects and desire for cocaine. Mazindol followed by cocaine administration was associated with larger and more sustained increases in heart rate and blood pressure as compared to cocaine alone. Mazindol was not found to alter subjective effects of cocaine. One subject had significant increases in heart rate and blood pressure during mazindol-cocaine administration, which continued for 3 hours. This subject also experienced anxiety and paranoia during the mazindol-cocaine condition. One 12-week, double-blind, placebo-controlled clinical trial of mazindol 2 mg daily in cocaine-dependent subjects has been reported (Stine et al. 1992) (table 7). Of 33 patients who consented to participate, 16 dropped out, and the average length of treatment was 5 weeks. Mazindol had no significant association with depression or anxiety symptoms, nor has this dose been associated with any reduction in cocaine use as measured by self-reports and urine toxicology screens.

Fluoxetine. Cocaine has been found to inhibit the uptake of serotonin (5-HT) two to four times more potently than that for DA (Ritz and Kuhar 1989). 5-HT synthesis or receptor blockade potentiates (but the 5-HT precursor, 5-hydroxytryptophan, antagonizes) cocaine-induced locomotor activity in animals (Cunningham et al. 1992). Studies have demonstrated that chronic cocaine administration results in a net decrease in 5-HT neurotransmission as a result of enhanced 5-HT autoregulatory mechanisms (Pradhan et al. 1978). This has been postulated to be a mechanism underlying the psychological consequences of chronic cocaine abuse. These findings have led to trials of medications with effects on central serotonergic regulation for the treatment of cocaine abuse. The drug in this class that has been studied most extensively is fluoxetine.

Several well-controlled clinical trials with fluoxetine have been conducted in patients with cocaine use disorders (table 7). One double-blind, placebo-controlled, crossover study (N = 5) determined the effects of treatment with 30 mg or 40 mg of fluoxetine followed by administration of IV cocaine (40 mg). Fluoxetine was associated with decreased "rush," magnitude of drug effect, drug liking, and "good effects." There was a negative correlation between response to the cocaine dose and plasma fluoxetine concentration, suggesting greater attenuation of cocaine effects with higher plasma fluoxetine levels (Walsh et al. 1992). A second study has been reported that examined the interaction of cocaine and fluoxetine in a dose-ranging study (N= 8) using fluoxetine 0, 20, 40, or 60 mg daily on an ascending schedule, with cocaine administration 0, 20, or 40 mg intravenously at each fluoxetine dose (Walsh et al. 1994*a)*. There was no evidence of cardiovascular toxicity under any of the

conditions. The 40 mg and 60 mg doses of fluoxetine were found to decrease subjective effects of cocaine. Fluoxetine has been utilized in outpatient clinical trials in both methadone-maintained, cocaine-dependent patients and in patients with primary cocaine use disorders. An open study in which methadone-maintained, cocaine-dependent patients were treated with a mean dose of fluoxetine 45 mg daily and followed with quantitative plasma and urine cocaine and BE concentrations showed a significant decrease in cocaine use by the end of the 9-week treatment period, though most subjects did not achieve abstinence (Batki et al. 1993). Urine BE concentration has been reported to correlate with patients' self-reports regarding cocaine use and craving (Batki et al. 1992). Fluoxetine has also been used as a treatment for primary cocaine dependence (Washburn et al. 1994). Subjects were randomized to receive fluoxetine 40 mg daily or placebo over a 12-week study period (N = 32). Subjects receiving fluoxetine remained in treatment for a significantly longer period of time (11 weeks versus 3 weeks) and remained abstinent for longer periods. An analysis of two double-blind, placebo-controlled trials in primary cocaine-dependent patients and secondary (methadone-maintained) cocaine-dependent patients showed that fluoxetine increased retention in primary cocaine-dependent outpatients and reduced cocaine use and craving in secondary cocaine dependence (Batki et al. 1994). These findings appear to indicate potential effectiveness of fluoxetine in the treatment of cocaine dependence.

Carbamazepine. Carbamazepine (CBZ) is an anticonvulsant medication hypothesized to have potential as a treatment for cocaine abuse because of its ability to block cocaine-induced "kindling" in rodents. Kindling has been postulated to be a model for the neurophysiological basis of cocaine craving. CBZ may also reverse the DA receptor supersensitivity that may result from chronic cocaine use, and its potential as a treatment for cocaine dependence has been examined in several studies (table 8). A double-blind, placebo-controlled, crossover study of the interaction of CBZ with cocaine in six cocaine users has been reported (Hatsukami et al. 1991). In this study, subjects were treated with CBZ 400 mg daily for 5 days, which was followed by administration of one 40 mg dose of smoked cocaine base. No changes in subjective responses to cocaine were observed, but significant increases in heart rate and diastolic blood

Carbamazepine (CBZ)

Rationale: Blocks cocaine-induced "kindling" in rodents; kindling has been proposed as a neurophysiological mediator of cocaine craving.

•(Hatsukami et al. 1991): Pretreatment of six cocaine users with CBZ 400 mg for 5 days followed by 40 mg smoked dose of cocaine; no change in subjective effects of cocaine; significant increases in heart rate and diastolic blood pressure.

•(Gorelick et al. 1994): CBZ did not alter self-administration of IV cocaine in cocaine-dependent subjects; CBZ levels of 1 to 3 or 4 to 7 &g/mL.

•(Halikas et al. 1993): CBZ 400 mg versus placebo as adjunct to psychosocial therapy, in sample of 183 cocaine abusers for 12 weeks, significant decrease in cocaine-positive urines and reported reduction in craving; CBZ levels not reported.

•(Montoya et al. 1993): CBZ versus placebo in sample of 62 cocaine- dependent patients for 8 weeks; CBZ levels 5.6 $\pm$ 0.8 &g/mL, no significant differences between CBZ and placebo-treated groups.

•(Kranzler and Bauer 1993) CBZ 400 to 600 mg versus placebo in 40 cocaine-dependent patients; no effect of CBZ on any measures (craving, cocaine use, paranoia during cocaine use, urine toxicology).

Naltrexone

Rationale: Opioid antagonist; opiate pathways may be involved in some of the reinforcing effects of cocaine; could potentially be blocked by naltrexone administration.

•(Kosten et al. 1992): 50 mg naltrexone or placebo daily for 10 days followed by IV cocaine administration (0.125 to 0.5 mg/kg); "dollar value" of cocaine decreased following naltrexone treatment; augmentation of heart rate but no effect on blood pressure for the naltrexone-cocaine condition.

•(Carroll et al. 1993): Open pilot of disulfiram and naltrexone for cocaine-dependent, alcohol abuse/dependent patients: naltrexone had no effect on cocaine or alcohol use.

•(Walsh et al. 1994*b*): Naltrexone in dose range 3.125 mg to 200 mg (weekly dose increases) had no effect on subjective or physiological effects of IV cocaine (0, 20, 40 mg).

pressure occurred. In another double-blind, placebo-controlled study that directly examined the safety and efficacy of CBZ in reducing cocaine use and craving, subjects were administered CBZ in dosages that resulted in plasma concentrations of either 1 to 3 mcg/mL (doses of 200 mg daily) or 4 to 7 mcg/mL (doses of 400 mg to 600 mg daily). CBZ did not alter cocaine self-administration or craving in these cocaine-dependent subjects. No evidence for safety problems or toxicity with the combination of cocaine and CBZ was observed in this study (Gorelick et al. 1994).

Several double-blind, placebo-controlled studies in outpatients with cocaine use disorders have been reported. In a 20-day, controlled, fixed-dose (CBZ 200 mg, 400 mg, or placebo) trial, 30 volunteers unmotivated for treatment and whose use of cocaine was unchanged from their usual during the study period were evaluated for cardiovascular effects before and during CBZ treatment. Systolic blood pressure was increased (2.1 mm Hg) and corrected QT intervals on electrocardiogram were shortened, while pulse was significantly increased (2.3 beats/minute), although all observations remained within normal limits throughout the study (Halikas et al. 1991). Several other studies have been conducted to determine the effectiveness of CBZ for the treatment of cocaine use disorders in outpatients. One study was conducted in which 183 subjects meeting diagnostic criteria for cocaine abuse were randomized to CBZ 400 mg or 800 mg daily or placebo as an adjunct to psychosocial therapy. CBZ 400 mg was associated with a significant decrease in cocaine-positive urines and a reduction in cocaine craving, and these findings were negatively correlated with CBZ level (Halikas et al. 1993). Another double-blind, placebo-controlled study that investigated the efficacy and safety of CBZ treatment in 62 subjects meeting diagnostic criteria for cocaine dependence found no significant difference in cocaine use, cocaine-positive urine samples, or depressive symptoms measured by the Beck Depression Inventory. Plasma CBZ levels of 5.6Å0.8 mcg/mL were achieved by week 4 of this study (Montoya et al. 1993). Another study examined CBZ 400 mg to 600 mg daily in 40 cocaine-dependent males over a 12-week study period. No significant effect of CBZ was observed for any of the outcome variables, which included self-reports of cocaine use, weekly urine for BE, cocaine craving, frequency or intensity of use, or cocaine-associated paranoia (Kranzler and Bauer 1993).

Naltrexone. Naltrexone is an opioid antagonist that has been examined as a treatment agent for cocaine abuse in several small studies to date (table 8). The rationale for use of naltrexone for cocaine addiction is that opiate pathways may be important to pleasurable or euphoric effects of cocaine; an antagonist of this pathway might decrease the reinforcing

effects of cocaine and, as a result, decrease cocaine use. This hypothesis is supported by primate studies in which an attenuation of cocaine self-administration was observed during naltrexone treatment (Mello et al. 1991). One study examined the self-reported and cardiovascular effects of intravenously administered cocaine (0.125, 0.25, 0.50 mg/kg) after 10 days of treatment with naltrexone 50 mg or placebo in a double-blind, randomized, within-subjects design (Kosten et al. 1992; Silverman et al. 1993). Cocaine-induced increases in self-reported dollar "value of cocaine" and "unpleasant" were less during naltrexone than placebo administration. Cocaine increased peak heart rate, and this elevation was augmented by naltrexone. Cocaine-induced alterations in blood pressure did not differ across naltrexone and placebo conditions. Another study examined the effects of a range of naltrexone doses (3.125 mg to 200 mg, with weekly dose increases) on the subjective and physiological effects of IV cocaine (0, 20, and 40 mg) (Walsh et al. 1994*b*). In this study, naltrexone had no effect on subjective or physiological responses to cocaine. One open pilot study compared the effectiveness of naltrexone 50 mg daily to that of disulfiram 250 mg daily for treatment of outpatients with cocaine dependence and alcohol abuse (Carroll et al. 1993). Naltrexone did not appear to impact cocaine or alcohol use in this study. Findings thus far with naltrexone indicate that it would be suitable for large, controlled outpatient trials to determine efficacy in the treatment of primary cocaine use disorders.

Disulfiram. Disulfiram is an inhibitor of aldehyde dehydrogenase that has been used in the treatment of selected patients with alcohol abuse or dependence. Three pilot studies have examined the efficacy and safety of disulfiram treatment for cocaine dependence (table 9). One recent study in six cocaine-dependent volunteers examined the effect of disulfiram 250 mg on responses to IN cocaine (2 mg/kg) using a randomized double-blind, placebo-controlled design (Hameedi et al. 1995; McCance-Katz et al. 1993). There was no significant difference in cocaine "high" or in physiological responses during disulfiram-cocaine administration as compared to cocaine alone. However, subjects reported decreased craving for cocaine when treated with disulfiram prior to cocaine administration. Additionally, several subjects reported significant dysphoria when disulfiram preceded cocaine administration. Plasma cocaine concentration following disulfiram and cocaine administration was significantly greater, and this may have contributed to the decreased craving and increased dysphoria observed in some subjects.

TABLE 9. *Cocaine antagonists.*

Disulfiram

Rationale: Many cocaine abusers are comorbid abusers of alcohol; use of alcohol leads to cocaine use in some persons and alcohol enhances euphoric effects and alleviates dysphoric effects of cocaine; inability to use alcohol with cocaine may decrease cocaine use.

•(Hameedi et al. 1995; McCance-Katz et al. 1993): Double-blind, randomized study of the effect of disulfiram 250 mg on IN cocaine administration (2 mg/kg); no effect on cocaine "high," but decreased craving, increased anxiety and paranoia, no evidence for toxicity based on cardiovascular responses.

•(Carroll et al. 1993): Open pilot study in 18 cocaine-dependent, alcohol-abusing outpatients found disulfiram 250 mg daily was associated with significantly less cocaine and alcohol use as compared to treatment with naltrexone 50 mg daily.

•(Van Etten et al. 1994): Open treatment of outpatients with cocaine dependence and alcohol abuse found a significant decrease in both cocaine (> twofold decrease in cocaine-positive urines) and alcohol use.

Another study reported on the effects of adjunct disulfiram therapy in outpatients meeting DSM-III-R criteria for cocaine dependence and alcohol abuse (Van Etten et al. 1994). Patients were treated for Æ 2 weeks on and off disulfiram 250 mg daily. Significantly fewer days of drinking and fewer drinks per occasion were reported during disulfiram treatment. A greater than twofold decrease in cocaine-positive urinalysis results was obtained during disulfiram treatment. An open pilot study has been reported in which 18 outpatients meeting diagnostic criteria for cocaine and alcohol dependence (but not physiologically dependent on alcohol) were randomized to treatment with disulfiram 250 mg daily or naltrexone 50 mg daily in conjunction with individual psychotherapy during a 12-week open trial (Carroll et al. 1993). Primary outcome measures included frequency and intensity of alcohol and cocaine use. Subjects self-reports of substance abuse were collected during weekly interviews with blind raters and verified by urine toxicology screens. Breathalyzer samples were obtained at each visit and all were negative.

Subjects treated with disulfiram reported significantly lower alcohol use days as compared to subjects taking naltrexone, fewer total days using alcohol, fewer total drinks during treatment, and more total weeks of abstinence. Cocaine use was also significantly reduced in the disulfiram group, with patients reporting a significantly lower percentage of cocaine use days, fewer days of cocaine use, and fewer observed positive urine screens for cocaine. Subjects reported fewer total grams of cocaine use and more total weeks of abstinence, although these differences were not statistically significant. One explanation for these results was that alcohol may be a powerful conditioned cue for cocaine craving and that disulfiram treatment may reduce exposure to alcohol, thereby arresting the chain of cues leading to cocaine use. In addition, findings from a study of simultaneous cocaine and alcohol administration (McCance-Katz et al. 1993) showed that cocaine abusers can reliably distinguish euphoria associated with combined cocaine-ethanol use from that of cocaine alone and prefer the combination. Disulfiram-maintained cocaine abusers may be less inclined to initiate cocaine use if they know they cannot potentiate cocaine euphoria or titrate negative acute cocaine effects through concurrent alcohol use. These findings indicate that disulfiram may have some efficacy in the treatment of cocaine dependence, but this remains to be confirmed in large, well-controlled outpatient trials.

FUTURE DIRECTIONS

A variety of drugs are being examined in preclinical studies and early clinical trials to determine their potential as medication treatments for cocaine dependence. These include drugs that might be expected to act as cocaine agonists, such as the DA uptake inhibitors, which have shown some promise in attenuation of cocaine effects in animal studies. Examples of such medications include benztropine (Acri et al. 1994), ifenprodil (Acri et al. 1994), and GBR 12909 (Char et al. 1994; Glowa et al. 1994) (table 10). Medications that might act as cocaine antagonists are also in preclinical and early clinical trials to examine potential safety and efficacy for treatment of cocaine dependence (table 10). One example of such a drug is the 5-HT_2 antagonist ritanserin. A single-blind trial conducted with eight cocaine-abusing volunteers pretreated with ritanserin, and who then participated in a cocaine administration study, has been reported (Sullivan et al. 1994). Ritanserin (5 mg and 10 mg) appeared to attenuate cocaine responses. Cocaine antagonist-type drugs might also include atypical neuroleptics such as risperidone or clozapine (Kosten and Nestler 1994) and the D_1 antagonist SCH23390 (Heidbreder and Shippenberg 1994). Human studies have been initiated to determine the effects of clozapine pretreatment on cocaine administration (F.

Hameedi, personal communication, October 1994). The N-methyl-D-aspartate (NMDA) (excitatory amino acid) antagonists dextrophan and dextromethorphan have also been studied in animals with some evidence for attenuation of expected cocaine effects (Sepinwall et al. 1992).

Although no medication has emerged that effectively treats the cocaine-dependent patient, research to date has yielded important information about the utility of numerous medications in the treatment of this disorder. As important, the work in this field has yielded information that will be critical to the design of future studies that will then provide even greater insights into the treatment of cocaine dependence. Preclinical studies continue to make inroads into understanding the complex neurobiological underpinnings of cocaine dependence and to identify promising new agents for study in clinical trials. The future of treatment for this widely prevalent and disabling disorder presents difficult challenges, but there are many possibilities for solutions that await further investigation.

TABLE 10. *Future directions.*

Cocaine agonists in preclinical studies

Rationale: Drugs with mild psychomotor stimulant effects (e.g., DA uptake inhibitors), but with other effects that may block the positive effects of cocaine or enhance the negative effects of cocaine.

•(Acri et al. 1994)

GBR12935: Potent and highly selective DA uptake inhibitor.

Benztropine: DA uptake inhibitor with muscarinic antagonist activity.

Ifenprodil: Inhibits DA uptake at concentrations comparable to those observed for cocaine.

GBR12935: Increased locomotor activity in mice; substituted for cocaine in rats trained to discriminate cocaine; enhanced cocaine effects; caused convulsions alone and in combination with cocaine.

TABLE 10. *Future directions (continued).*

Ifenprodil: Attenuated stimulant effects of cocaine at doses that did not reduce spontaneous activity when given alone.

Benztropine: Increased locomotor activity in mice and substituted for cocaine in rats trained to discriminate

cocaine; overall low efficacy as a stimulant, reduced ability to enhance behavioral effects of cocaine, no evidence of toxicity alone or with cocaine.

•(Glowa et al. 1994)
GBR 12909: Decreased cocaine responding in monkeys and was not self-administered by cocaine naive monkeys.

Cocaine antagonists in preliminary studies

Rationale: Blockade of cocaine pharmacological effects by treatment with drugs with specific targets may alter acute cocaine effects.

•(Kosten and Nestler 1994)
Clozapine: An atypical neuroleptic has been shown to inhibit cocaine-conditioned place preference.

•(Heidbreder and Shippenberg 1994)
SCH23390: A D_1 antagonist that has been shown to attenuate cocaine effects in an animal model.

•(Sepinwall et al. 1992)
Dextrophan and dextromethorphan: NMDA antagonists that have shown some evidence for attenuation of cocaine effects in animal studies.

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Click here to go to page 73