

## The Search for Medications to Treat Stimulant Dependence

Progress in understanding the neurobiology of stimulant dependence has enabled researchers to identify medications whose pharmacological effects suggest that they might help patients initiate abstinence or avoid relapse. Several of these medications and a vaccine have shown encouraging results in controlled clinical trials with cocaine-dependent patients. The search for a medical treatment for methamphetamine dependence started more recently, due to the later emergence of this epidemic, but at least one candidate medication has shown promise in early clinical testing. Treatment approaches that combine efficacious medications and empirically proven behavioral interventions, such as voucher-based reinforcement therapy, will almost certainly produce the best results.

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The demand for treatment for cocaine dependence remained roughly level from 1992 to 2005, while the demand for treatment for amphetamine dependence increased about eight-fold (Substance Abuse and Mental Health Services Administration, 2006). Although progress has been made in developing new psychosocial treatments for stimulant dependence, many patients do not substantially benefit from psychotherapy alone. Dropout rates in cocaine dependence treatment programs frequently exceed 50 percent (Alterman et al., 1996). Thus, the identification of medications to augment psychosocial treatment is an urgent research priority. Progress in understanding the neurobiology of stimulant dependence has led to the identification of several medications whose effects counter or alleviate the disordered processing that underlies patients' symptoms. Depending on their specific actions, these medications may help patients attain an initial period of abstinence or avoid relapse (Table 1). Although none has yet been approved for treating stimulant dependence, several have shown encouraging results in controlled clinical trials.

### ABSTINENCE INITIATION

Cocaine withdrawal symptoms, including dysphoric mood, fatigue, sleep disturbance, appetite changes, and irritability, contribute to many dependent patients' difficulties quitting the drug. Several studies have demonstrated that patients who experience severe cocaine withdrawal symptoms, as measured by the Cocaine Selective Severity Assessment (CSSA), are twice as likely to drop out of treatment and less likely to attain abstinence in outpatient programs (Kampman et al., 2001).

TABLE 1. Candidate Medications for Stimulant Dependence

MEDICATION	THERAPEUTIC EFFECT/MECHANISM OF ACTION
<b>Abstinence Initiation Medications</b>	<b>Ameliorate withdrawal symptoms, reduce cocaine reinforcement</b>
Modafinil	Acts as a mild stimulant, countering energy depletion during withdrawal; blocks cocaine-induced euphoria/enhances glutamate transmission
Propranolol	Reduces anxiety during withdrawal; may blunt cocaine-induced euphoria and craving/reduces sensitivity to adrenaline
Bupropion	Eases negative mood symptoms of withdrawal/inhibits dopamine reuptake
<b>Relapse Prevention Medications</b>	<b>Reduce cocaine reinforcement or increase unpleasant effects</b>
GABA Enhancers	Inhibit cocaine reinforcement by elevating GABA, a neurotransmitter that opposes the cocaine-induced dopamine surge that underlies reward
GVG	/Inhibits breakdown of GABA by the enzyme GABA transaminase
Tiagabine	/Blocks GABA reuptake via the presynaptic GABA transporter type 1
Topiramate	/Directly facilitates GABA neurotransmission; inhibits glutamate, which opposes GABA's effect on dopamine
Disulfiram	Increases cocaine-induced anxiety/blocks enzymatic degradation of dopamine and cocaine
TA-CD Vaccine	Inhibits all cocaine-induced psychoactive effects/stimulates production of cocaine-specific antibodies that prevent cocaine from crossing the blood–brain barrier

Abbreviations: GVG, gamma-vinyl gamma-aminobutyric acid; GABA, gamma-aminobutyric acid.

An apparent clinical basis for these associations is that patients who are subject to severe symptoms may keep taking the drug to avoid them. Investigators also have noted that these individuals report more intense highs from experimentally administered cocaine (Sofuoglu et al., 2003; Figure 1) and therefore may experience greater drive to keep taking it.

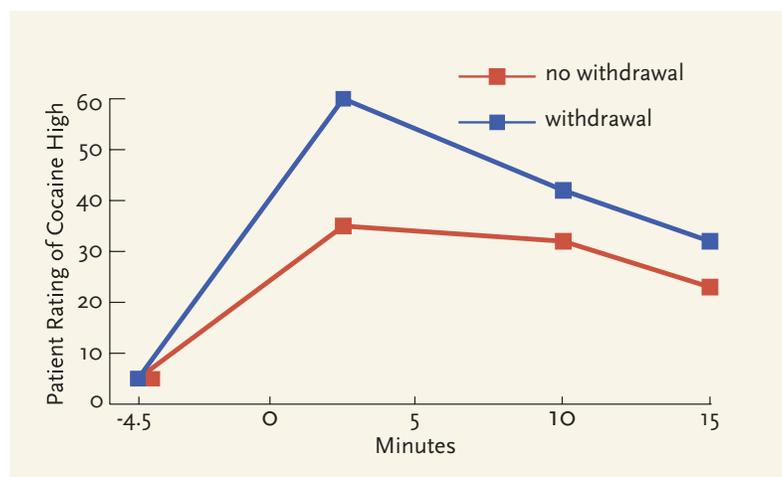
### Modafinil

The most promising medication for abstinence initiation is modafinil, a medication currently approved for the treatment of narcolepsy. Modafinil has several characteristics that might facilitate abstinence from cocaine. As a mild stimulant, it may reduce cocaine withdrawal symptoms (Dackis and O'Brien, 2003). As an enhancer of glutamate neurotransmission, it may ameliorate the glutamate depletion seen in chronic cocaine users (Dackis and O'Brien, 2003); improved baseline glutamatergic tone in the nucleus accumbens prevented reinstatement of cocaine self-administration in an animal model of

relapse (Baker et al., 2003).

Modafinil has been shown to block the euphoric effects of cocaine in three independent human laboratory studies. In the first, pretreatment with 400 mg of modafinil blunted euphoria from a subsequent intravenous dose of cocaine (30 mg) when compared with pretreatment with 200 mg of modafinil or placebo (Dackis et al., 2003). In a similar study, patients given 400 or 800 mg of modafinil reported lower ratings of “high,” “any drug effect,” and “worth in dollars” in response to a subsequent dose of cocaine, compared with patients who received cocaine alone (Malcolm et al., 2006). Most recently, Hart and colleagues (2008) evaluated the effect of modafinil maintenance (200 or 400 mg/day) on eight non-treatment-seeking cocaine-dependent individuals' responses to smoked cocaine (at 0, 12, 25, and 50 mg). Modafinil at both dosages attenuated the participants' frequency of self-administration, subjective ratings of cocaine's effects, and cocaine-related increases in heart rate and blood pressure.

FIGURE 1. A Tighter Vise



Individuals who experience more intense highs from cocaine tend to suffer more severe withdrawal symptoms. Quitting cocaine may be more difficult for them, because it involves greater sacrifice of pleasure and more physical and mental distress. (Adapted from Sofuoglu et al., 2003, with permission from Elsevier.)

Modafinil improved cocaine abstinence rates in two clinical trials. In a double-blind pilot trial with 62 cocaine-dependent patients, those who received modafinil submitted more cocaine-metabolite-free urine samples than placebo-treated patients (42 vs. 22 percent; Dackis et al., 2005). Modafinil-treated patients were also deemed more improved on the clinician-rated portion of the Clinical Global Impression Scale (CGIS). The results of the pilot trial were replicated in a recent multicenter trial. Over 16 weeks, 210 cocaine-dependent patients took 200 mg of modafinil daily, 400 mg of modafinil daily, or placebo. Among patients who were dependent only on cocaine, both dosages of modafinil were superior to placebo for promoting abstinence (Dackis, 2007). This trial also included patients (41 percent) who were dually dependent on cocaine and alcohol; their abstinence rates were not increased by modafinil. Two more large-scale double-blind, placebo-controlled clinical trials of modafinil are ongoing.

Modafinil promotes wakefulness and may cause insomnia. Clinicians are advised to avoid its use in patients with bipolar disorder or psychosis, as it may exacerbate symptoms of mania and psychosis. Nor should it be used in patients with left ventricular hypertrophy or mitral valve prolapse, as patients with these conditions developed potentially serious adverse effects in clinical trials.

### Propranolol

The beta blocker propranolol has shown promise for the treatment of patients with severe cocaine withdrawal

symptoms. Beta blockers are used primarily to treat angina and hypertension, but their primary pharmacological effect—reducing the impact of the neurotransmitter adrenaline—also reduces anxiety. The distressing anxiety and agitation experienced by cocaine-dependent patients during withdrawal appears to be due to heightened sensitivity to the effects of adrenaline and noradrenaline. For example, McDougle and colleagues (1994) demonstrated that giving cocaine-dependent patients yohimbine, a compound that increases adrenaline in the central nervous system, provoked significantly more anxiety during cocaine withdrawal. Along with potential efficacy against withdrawal-related anxiety, propranolol may lessen some of cocaine's rewarding properties and more uncomfortable symptoms of craving. In a human laboratory trial, the beta blocker carvedilol reduced cocaine self-administration in non-treatment-seeking cocaine-dependent subjects (Sofuoglu et al., 2000).

Three clinical trials have suggested that propranolol may help patients with severe cocaine addiction to remain in treatment and to establish initial abstinence. In the first, a pilot trial in which participants knew what medication they were receiving, propranolol proved safe and was well-tolerated (Kampman et al., 1999). Compared with a historical control group, more propranolol-treated patients (80 vs. 47 percent) stayed in treatment throughout a 7-week outpatient program. In a subsequent double-blind, placebo-controlled trial, propranolol improved treatment retention and decreased cocaine use among 108 patients with severe cocaine withdrawal symptoms, as determined by a score of 27 or more on the CSSA (Kampman et al., 2001). In the most recent trial, propranolol appeared to promote abstinence from cocaine in a trial of 199 patients who entered treatment with severe cocaine withdrawal symptoms (Kampman et al., 2006). Among patients adherent to the study medications, about 24 percent of the propranolol-treated patients were abstinent from cocaine at week 10, as opposed to only 12.5 percent of placebo-treated patients.

Propranolol is usually well-tolerated. The main side effect is sedation. However, beta blockers are best avoided in patients with a history of cocaine-induced cardiac ischemia. Patients who have presented to a medical facility with complaints of chest pain associated with cocaine use have been excluded from all clinical trials of propranolol for cocaine dependence and should not be treated with propranolol.

## RELAPSE PREVENTION

Once cocaine-dependent patients have attained a period of abstinence, a more difficult phase of treatment, relapse prevention, begins. Pharmacological strategies for relapse prevention aim to block cocaine-induced euphoria or reduce cocaine craving. New insights into the effects of cocaine on the brain reward system have led to the identification of several promising medications.

Cocaine causes euphoria and reinforcement by raising dopamine levels in the mesocortical reward system. One potential way to counterbalance this effect is to elevate mesocortical levels of gamma-aminobutyric acid (GABA), a neurotransmitter that pushes dopamine levels downward by inhibiting the activity of dopaminergic (dopamine-releasing) neurons. Preclinical trials have suggested that GABAergic compounds (i.e., compounds that promote GABA release or conservation) blunt the dopamine response to cocaine administration and conditioned reminders of prior cocaine use (Dewey et al., 1997) and reduce self-administration of cocaine in animal models (Kushner, Dewey, and Kornetsky, 1999). Accordingly, GABAergic medications are being tested as potential agents to prevent relapse by blocking cocaine-induced euphoria or reducing cue-induced craving caused by reminders of prior cocaine use. Some promising GABAergic medications include gamma-vinyl GABA (GVG), tiagabine, and topiramate.

### Gamma-Vinyl GABA

GVG is an antiepileptic that elevates brain GABA concentrations by inhibiting an enzyme, GABA transaminase, that breaks down the neurotransmitter. In preclinical trials, GVG has reduced rodents' self-administration of cocaine (Kushner, Dewey, and Kornetsky, 1999), amphetamine, and methamphetamine (Gerasimov et al., 1999).

GVG has demonstrated potential efficacy for the treatment of stimulant dependence in the two clinical trials, both open-label, that have addressed this question to date. Eight of 20 patients completed the first trial and reported drug-free periods ranging from 46 to 58 days (Brodie, Figuero, and Dewey, 2003). Eighteen of 30 subjects completed the second trial; 16 of the completers submitted drug tests negative for amphetamine and cocaine throughout the last 6 weeks of the trial (Brodie et al., 2005).

Although GVG is used in many countries, it has not been approved for use in the United States because of an association with visual field defects. Data suggest that

this adverse effect occurs only after relatively long-term exposure, so brief treatments may be conducted safely (Schmitz et al., 2002). As a precaution, investigators in the second clinical trial of GVG for stimulant dependence used perimetry to assess for potential visual field defects; none occurred (Fechtner et al., 2006).

Although GVG is grouped here with medications to prevent relapse, it might be considered for abstinence initiation as well. The clinical trials cited earlier were conducted in patients who had not achieved sustained abstinence. Large-scale, well-controlled trials of GVG for both cocaine and amphetamine dependence are planned.

### Topiramate

The pharmacological effects of topiramate appear particularly well-suited for preventing relapse to cocaine use. In addition to increasing cerebral levels of GABA and facilitating GABA neurotransmission (Kuzniecky et al., 1998), topiramate weakens the action of glutamate, a neurotransmitter that opposes GABA's potentially therapeutic reduction of dopamine activity. Topiramate's exact mechanisms of action on GABA are not fully understood, but it is known to inhibit glutamate neurotransmission by blocking alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate receptors (Gibbs et al., 2000). In animal models of cocaine relapse, blockade of AMPA receptors in the nucleus accumbens prevented reinstatement of cocaine self-administration (Cornish and Kalivas, 2000).

In a 13-week, double-blind, placebo-controlled pilot trial of topiramate involving 40 cocaine-dependent patients, those who received topiramate were more likely than controls who received placebo to be abstinent during the last 5 weeks of treatment (Kampman et al., 2004). Among patients who returned for at least one visit after receiving medications, more of those on topiramate achieved at least 3 weeks of continuous abstinence (59 vs. 26 percent), and more in this group were rated very much improved on the CGIS at their last visit (71 vs. 32 percent; Kampman et al., 2004).

Topiramate can cause sedation and memory problems, especially if the dose is titrated rapidly. Prescribing criteria contraindicate its use in patients with a history of kidney stones. Drug blood levels of patients with reduced renal function should be monitored, as the drug is excreted by the kidneys. Rare but serious complications of topiramate include metabolic acidosis, acute glaucoma, and oligohydrosis (decreased sweating).

Pharmacological studies for relapse prevention aim to block euphoria or reduce craving.

Similarities between the mechanisms of action of amphetamine and those of cocaine suggest that the same medications may help with both dependencies.

### Tiagabine

Tiagabine, a medication currently approved for treatment of seizures, raises brain GABA levels by selectively blocking the presynaptic GABA reuptake transporter type 1. Tiagabine was found to be well-tolerated and moderately effective for improving abstinence in a pilot study with 45 cocaine- and opiate-dependent patients participating in a methadone maintenance program (Gonzalez et al., 2003). In this 10-week trial, the number of urine samples free of cocaine metabolite increased by 33 percent in a group treated with 24 mg of tiagabine daily, while decreasing by 14 percent in a placebo-treated group.

### Disulfiram

Disulfiram (Antabuse), a medication that is familiar to substance abuse clinicians as a treatment for alcohol dependence, is a promising cocaine relapse prevention medication with a unique mechanism of action. Disulfiram blocks the enzymatic degradation of cocaine and dopamine, leading to extremely high cocaine and dopamine levels when cocaine is ingested (McCance-Katz, Kosten, and Jatlow, 1998). However, rather than increase the cocaine-induced high, as one might expect, this effect makes the high less pleasant by increasing the associated anxiety. Four published trials have demonstrated that disulfiram reduces cocaine use in cocaine-dependent patients: Carroll et al., 1998 (cocaine- and alcohol-dependent patients); Carroll et al., 2004 (patients dependent on cocaine only); George et al., 2000 (cocaine- and opiate-dependent patients); Petrakis et al., 2000 (cocaine- and opiate-dependent patients).

Disulfiram is generally well-tolerated, although it may cause side effects, including sedation, headache, or a metallic taste in the mouth. If disulfiram is eventually approved for treating cocaine dependence, patients will need to be educated about its effects on cocaine metabolism and the potential danger of using disulfiram and the drug together. Patients also should be told that they may experience an unpleasant reaction (caused by the medication's blockade of an enzyme, aldehyde dehydrogenase, and consequent buildup of acetaldehyde) if they drink alcohol. Disulfiram is contraindicated in patients who have severe myocardial disease or coronary occlusion; who have psychoses; and those who are receiving or those who have recently received metronidazole, paraldehyde, alcohol, or alcohol-containing products.

### TA-CD Vaccine

Another promising relapse prevention therapy currently being explored is a vaccine. TA-CD works by stimulating the production of cocaine-specific antibodies that bind to cocaine molecules and prevent them from crossing the blood-brain barrier, thereby blunting the drug's euphoric and reinforcing effects. In laboratory trials, TA-CD decreased rodents' self-administration of cocaine (Kantak et al., 2000).

The vaccine has shown promise in human trials. In one of the first, TA-CD was administered to 34 cocaine-dependent inpatients. A series of three vaccinations resulted in high antibody titers, and the vaccine was well-tolerated (Kosten et al., 2002). More recently, two doses of TA-CD were tested in cocaine-dependent patients in a 12-week outpatient treatment program. Preliminary outcome data suggested that the vaccine reduced the euphoric effects of cocaine; the higher dose was associated with more cocaine abstinence compared with the lower dose (Martell et al., 2005).

## MEDICATIONS FOR AMPHETAMINE DEPENDENCE

The search for medications to treat amphetamine and methamphetamine dependence started much more recently than that for cocaine treatment medications. Consequently, fewer medications have been tested. Similarities between the mechanisms of action of amphetamine and methamphetamine and those of cocaine suggest that the same medications may help with both dependencies. Hence, several of the medications that have been discussed are undergoing, or about to undergo, testing for methamphetamine dependence. For instance, trials of topiramate and modafinil are planned.

Bupropion is an antidepressant medication that is also effective in smoking cessation. Bupropion's efficacy for these uses rests upon its ability to support positive mood by inhibiting the reuptake of dopamine into cells, leaving more of the neurotransmitter circulating in the mesolimbic system. The same mechanism may be helpful in easing the negative mood symptoms of methamphetamine withdrawal.

Although studies have shown bupropion to be ineffective in treating cocaine dependence, a recent clinical trial suggested that it may have promise for methamphetamine dependence. Among 151 methamphetamine-dependent patients, bupropion recipients had somewhat better abstinence outcomes compared with placebo recipients; the difference approached, but did

not quite achieve, statistical significance. In a subgroup of patients whose methamphetamine use at baseline was less intensive, however, bupropion treatment was associated with significantly more weeks of abstinence (Elkashaf et al., 2007).

Bupropion is fairly well-tolerated. Common side effects include insomnia, agitation, dry mouth, and nausea. This medication is contraindicated in patients with seizure disorders, current or prior diagnoses of bulimia or anorexia nervosa, or concurrent treatment with (or within 14 days of discontinuation of) monoamine oxidase inhibitors. Bupropion should not be used in patients detoxifying from alcohol or sedatives.

### MEDICATIONS AND VOUCHER-BASED REINFORCEMENT THERAPY

Voucher-based reinforcement therapy (VBRT) is a behavioral treatment in which substance-dependent patients who achieve predetermined therapeutic goals receive vouchers redeemable for goods and services in the community. VBRT has been shown to be highly effective for helping cocaine-dependent patients achieve initial abstinence (Higgins et al., 1994). Several recent trials have indicated that VBRT may be a highly effective psychosocial treatment platform for enhancing the efficacy of medications for the treatment of cocaine dependence. For example, Kosten and colleagues (2003) gave desipramine, an antidepressant, or placebo with VBRT or a noncontingent voucher control to cocaine- and opiate-dependent patients who were being maintained on buprenorphine. The patients given either desipramine or VBRT increased their frequency of urine samples containing no abused drug more rapidly than patients given neither, and those treated with both desipramine and VBRT produced the most such samples of any group (Kosten et al., 2003). These findings contrast with those of trials in the 1980s, which demonstrated that desipramine in combination with standard psychosocial treatment was ineffective in this population.

In another double-blind trial, bupropion plus VBRT was found to be superior to bupropion or VBRT alone, or placebo, in promoting abstinence from cocaine (Poling et al., 2006). Similar results were reported for the combination of the serotonin reuptake inhibitor (SRI) citalopram and VBRT (Moeller et al., 2007). Like desipramine, SRIs have not been found to be consis-

tently efficacious for the treatment of cocaine dependence when used in association with standard psychosocial treatment.

The best way to integrate effective medications and psychotherapies into a comprehensive plan for the treatment of stimulant dependence has yet to be determined. One can imagine a treatment course that begins with an abstinence initiation medication and contingency management, then switches to relapse prevention medications when the patient reaches some significant abstinence milestone. Alternatively, a patient might continue to receive an abstinence initiation medication that is at some point supplemented with either a relapse prevention medication that is slowly titrated upward or with TA-CD immunization. How long medication treatment should be continued is another unanswered question. Studies to address these questions are being considered, but, for now, there are no data.

### CONCLUSIONS

Currently, no medications are approved by the Food and Drug Administration for the treatment of stimulant dependence. However, recent advances in understanding the processes involved in cocaine addiction have allowed researchers to identify several promising candidates (Table 2). Many of these medications have already shown promise in double-blind, placebo-controlled clinical trials, and virtually all of them are undergoing confirmatory testing. Behavioral and psychosocial treatments, especially VBRT, may augment the efficacy of medication for the treatment of stimulant dependence.

Clinicians should be aware that all of the trials to date have been relatively small; therefore, the efficacy and safety of these medications have not been established definitively. In addition, most of the trials have included primarily men; thus, efficacy in women is even less well-established. Although no medications are currently proven to be effective, it is hoped that effective pharmacological treatments for stimulant dependence will soon become available.

### CORRESPONDENCE

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Currently, no medications are approved by the FDA for the treatment of stimulant dependence.

TABLE 2. Summary of Controlled Clinical Trials of Medications for Cocaine and Methamphetamine Dependence

MEDICATION, DAILY DOSE, AND OTHER TREATMENTS	N	DURATION, WEEKS	DEPENDENCE DIAGNOSIS	OUTCOME	REFERENCE
Modafinil 400 mg vs. placebo	62	8	Cocaine-dependent	Cocaine-negative urine drug screens were significantly higher in the modafinil group than in the placebo group (42 vs. 22 percent).	Dackis et al., 2005
Propranolol 100 mg vs. placebo	108	8	Cocaine-dependent with severe cocaine withdrawal symptoms	Among patients who entered treatment with more severe cocaine withdrawal symptoms, mean urinary benzoylcegonine levels were lower in propranolol-treated patients than in placebo-treated patients.	Kampman et al., 2001
Propranolol 100 mg vs. placebo	199	10	Cocaine-dependent with severe cocaine withdrawal symptoms	The odds of cocaine abstinence, determined by thrice-weekly urine drug screens, improved significantly over time in propranolol-treated patients but not in placebo-treated patients. This effect was most prominent in patients who took at least 80 percent of the prescribed study medication.	Kampman et al., 2006
GVG 2 g (open label)	20	9	Cocaine- or methamphetamine-dependent	Eight of 20 subjects completed the trial and self-reported periods of abstinence ranging from 46 to 58 days.	Brodie, Figuero, and Dewey, 2003
GVG 2 g (open label)	30	9	Cocaine- or methamphetamine-dependent	Of the 18 subjects who completed the trial, 16 submitted drug tests negative for amphetamine and cocaine over the last 6 weeks of the trial.	Brodie et al., 2005
Topiramate 200 mg vs. placebo	40	13	Cocaine-dependent	Measured by twice-weekly urine drug screens, the likelihood of abstinence after week 8 was significantly greater in topiramate-treated patients than in placebo-treated patients.	Kampman et al., 2004
Tiagabine 12 or 24 mg vs. placebo	45	10	Cocaine- and opiate-dependent, maintained on methadone	During weeks 9 and 10, cocaine-free urine samples increased from baseline by 33 percent in the group taking 24 mg of tiagabine, increased by 14 percent in the group taking 12 mg of tiagabine, and decreased by 10 percent in the placebo group.	Gonzalez et al., 2003
Disulfiram 250-500 mg vs. psychotherapy control	122	12	Cocaine and alcohol abusers	Disulfiram treatment was associated with more consecutive weeks of abstinence than was psychotherapy alone.	Carroll et al., 1998
Disulfiram 250 mg vs. placebo	20	12	Cocaine- and opiate-dependent, maintained on buprenorphine	The total number of weeks of cocaine abstinence, verified by thrice-weekly urine drug screens, was significantly higher in disulfiram-treated patients than in placebo-treated patients (7.8 vs. 3.3).	George et al., 2000
Disulfiram 250 mg vs. placebo	67	12	Cocaine- and opiate-dependent, maintained on methadone	Self-reported cocaine and alcohol use was significantly lower in disulfiram-treated patients than in placebo-treated patients.	Petrakis et al., 2000
Disulfiram 250 mg vs. placebo	121	12	Cocaine-dependent	Self-reported cocaine use was significantly lower in disulfiram-treated patients than in placebo-treated patients. The disulfiram-treated group was significantly more likely to submit a cocaine-negative urine drug screen.	Carroll et al., 2004
TA-CD 400 µg vs. TA-CD 2,000 µg	18	14	Cocaine-dependent	The group administered 2,000 µg of TA-CD was significantly more likely to maintain cocaine-free urine samples than the group administered 400 µg.	Martell et al., 2005
Bupropion 300 mg vs. placebo	151	12	Methamphetamine-dependent	Among patients who used methamphetamine 18 days or less in the 30 days prior to the trial, significantly more bupropion-treated patients had a methamphetamine-free week (56 percent) than placebo-treated patients (40 percent), based on urine drug screen results.	Elkashef et al., 2007
Desipramine 150 mg + VBRT-C vs. VBRT-C alone vs. desipramine 150 mg + NCV vs. placebo + NCV	160	12	Cocaine- and opiate-dependent, maintained on methadone	The group receiving voucher-based reinforcement and desipramine had more drug-free urine samples (50 percent) than the other three groups (25-29 percent).	Kosten et al., 2003
Bupropion 300 mg + VBRT-CO vs. VBRT-CO alone vs. bupropion 300 mg + NCV vs. placebo + NCV	106	25	Cocaine- and opiate-dependent, maintained on methadone	Patients receiving voucher-based reinforcement and bupropion had significantly fewer cocaine-positive urine drug screens than the other three groups.	Poling et al., 2006
Citalopram 20 mg + VBRT-C vs. placebo + VBRT-C	76	12	Cocaine-dependent	Citalopram-treated patients had a significantly lower probability of submitting a cocaine-positive urine sample than the placebo-treated patients.	Moeller et al., 2007

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