DISEASES AND DISORDERS

The treatment of cocaine use disorder

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Cocaine use continues to be a serious worldwide public health problem. Cocaine abuse is associated with substantial morbidity and mortality. Cocaine overdose deaths are increasing in the United States and, in certain populations, outnumber heroin and opiate overdose deaths. Psychosocial treatments remain the treatments of choice for cocaine use disorder (CUD), with standard approaches including contingency management and cognitive behavioral therapy. However, the effect sizes of these treatments are not large, and they are not effective for most patients. Consequently, investigators have sought to develop pharmacological agents to augment the efficacy of psychosocial treatments. Despite these efforts, no medications have yet been proven to be safe and effective for the treatment of CUD. The most promising pharmacological strategies for CUD treatment thus far include the use of dopamine agonists, such as long-acting amphetamine and modafinil or glutamatergic and GABAergic agents such as topiramate. Combination drugs may be especially promising.

INTRODUCTION

With approximately 2.2 million regular users of cocaine in the United States, and 1 million individuals with cocaine use disorder (CUD) in the past year (*1*), CUD is a serious public health problem. Use of cocaine, including crack cocaine, is associated with substantial morbidity and elevated rates of health care utilization (*2*), and deaths associated with cocaine use are increasing. In the United States, the marked increase in overdose deaths in the past decade has been attributed largely to opioid overdose deaths. However, deaths from cocaine overdose doubled between 2011 and 2016 (*3*); in non-Hispanic black men and women, the death rate from cocaine overdose exceeded that from opiate overdose (*4*). Even in the current era of increasing opioid use and associated opioid overdose deaths, cocaine use remains a serious problem. Development of effective treatments for CUD is therefore a clinical priority.

Because no medications have been approved for the treatment of CUD, psychosocial treatment is currently the standard treatment. Several types of psychosocial treatments for CUD have proven efficacy. Group counseling and individual drug counseling are the most common treatments. Cognitive behavioral therapy (CBT) and motivational interviewing have also been shown to be effective. Perhaps the most effective psychosocial treatment for CUD is contingency management (CM), using voucher-based reinforcement. In this treatment, patients receive vouchers redeemable for goods and services in the community, contingent upon achieving a predetermined therapeutic goal. CM treatment has been found to be especially effective in promoting initial abstinence from cocaine.

Despite progress in the development of psychosocial treatments for CUD, many patients still do not respond to these treatments. Standard treatment for CUD has been associated with high dropout rates, and many patients do not attain substantial periods of cocaine abstinence. This limitation has stimulated the search for pharmacological approaches for the treatment of CUD. Despite several decades of study, however, no medication has yet been approved for the treatment of CUD. CUD is a heterogeneous disorder that has so far not responded to pharmacotherapeutic interventions. Progress in the understanding of the neurobiology of CUD has led to the discovery of several promising medications that have shown encouraging results in controlled clinical trials. Among the most promising medications have been dopamine agonists, including long-acting amphetamine, and modafinil and γ-aminobutyric acid (GABA)/glutamatergic medications including topiramate. Combinations of medications such as topiramate and mixed amphetamine salts also appear promising.

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PSYCHOSOCIAL INTERVENTIONS

The most common treatment for CUD is a combination of group, individual, and sometimes family therapy provided in several sessions per week, known as intensive outpatient therapy (IOT). IOT was shown to be as effective as inpatient drug treatment for the initial treatment of CUD in the early 1990s and was found to be a cost-effective way to treat the large number of patients with CUD who presented for treatment during that era (*5*). Although the specific procedures of IOT vary from program to program, most IOT programs consist of a combination of group and individual drug counseling, along with varying degrees of family involvement. Standard outpatient drug counseling typically consists of one or two sessions per week; the duration of an individual counseling session is typically between 30 and 60 min, while group sessions are 60 to 90 min in length. IOT treatments typically provide 9 hours of treatment contact per week. Participation in mutual help groups (such as 12-step meetings) is generally encouraged.

The efficacy of IOT treatment has been demonstrated in a number of clinical trials (*6*–*8*). What has not been established is the intensity of treatment necessary to support substantial reductions in CUD symptoms. Clinical trials suggest that treatments involving multiple sessions per week are more effective than those with one session per week. A multisite natural cohort analysis of 918 subjects with *DSM-IV* (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*) cocaine dependence compared 338 subjects receiving IOT (more than 9 hours per week) with 580 patients receiving standard treatment (one or two sessions up to 4 hours per week) over a period of 6 months. Both test groups experienced reduced drug use during the trial, with no differences in drug use between the two groups (*9*). Coviello *et al.* (*8*) compared a 12-hour/week IOT and a 6-hour/week standard outpatient treatment. At 7 months posttreatment,

subjects in both groups showed a 52% reduction in days of cocaine use, and both groups also showed improvement in psychiatric functioning and employment status; there were no differences in any outcomes between groups (*8*). Patients with CUD appear to fare better when they are seen several times per week compared to once a week, but IOT can provide some benefit even in relatively low–intensity treatments.

Despite showing reduction in cocaine use overall, many patients do not respond to standard addiction treatments and there are often high dropout rates (*10*). There are several promising alternatives to standard psychosocial treatment, of which two of the most effective include voucher-based reinforcement therapy (VBRT) and CBT. VBRT is the most effective treatment for promoting abstinence, and CBT has shown particular benefit for relapse prevention.

For promoting abstinence in patients with CUD, no therapy has been shown to be more effective than VBRT, especially when VBRT is coupled with community reinforcement therapy. VBRT is based on the behavioral principle that a behavior that is rewarded is more likely to be repeated. In VBRT, patients receive vouchers redeemable for goods and services in the community contingent upon achieving a predetermined therapeutic goal, such as drug abstinence. Using CM in the form of VBRT reinforces new adaptive behaviors that conflict with addictive behavior. VBRT is delivered as a component of a psychosocial treatment, such as IOT or drug counseling, CBT or community reinforcement therapy, rather than alone.

Several randomized trials have shown VBRT to be efficacious in promoting initial abstinence in cocaine users in outpatient treatment (*11*–*15*). For example, Higgins *et al.* (*12*) randomly assigned 40 cocaine-dependent subjects to receive behavioral therapy with or without VBRT for 12 weeks, followed by an additional 24 weeks of behavioral therapy alone. After 24 weeks, the average duration of cocaine abstinence was greater for the VBRT group compared with the control group (11.7 weeks versus 6.0 weeks) (*12*). In another trial, 37 cocaine- and opiate-dependent patients treated with methadone maintenance were randomly assigned to VBRT versus a control treatment (*13*). Subjects assigned to the VBRT compared with the control group were more likely to be cocaine abstinent during the 12-week trial and were more likely to achieve 2 weeks or more of sustained cocaine abstinence (47% versus 6%).

A disadvantage of VBRT is often cost. However, lower-cost variants of VBRT using intermittent reinforcement, such as the "fishbowl" technique, have been shown to be effective (*16*). In the fishbowl technique, patients are rewarded for achieving abstinence by being allowed to draw from a fishbowl in which they are likely to not only achieve a smaller reward but also have a chance at receiving a much larger reward.

Another limitation of VBRT (and other methods of CM) is that the positive effects of the intervention on cocaine abstinence are not long lasting, fading after the reinforcers are removed (*17*). VBRT may be best used in conjunction with other therapies, such as CBT, that are more likely to achieve long-term outcomes. For example, one clinical trial compared 16 weeks of treatment with CM, CBT, or a combination of the two interventions in 171 patients with *DSM-IV* stimulant dependence. Patients assigned to CM had higher rates of treatment retention and lower rates of stimulant use compared with the CBT and combined-treatment groups during the treatment period (*11*). Stimulant use outcomes were comparable among all test groups at 6- and 12-month follow-up.

CBT focuses on reducing or avoiding drug craving. Patients are taught to recognize the situations or states associated with prior drug use that provoke drug craving and to avoid these situations whenever possible. Patients are also taught a variety of coping skills to use when cocaine craving occurs, such as distraction, recall of negative consequences, and positive thought substitution (*18*).

Clinical trials in patients with *DSM-IV* cocaine dependence suggest that CBT is efficacious compared with more standard psychosocial treatments. First, in a trial comparing CBT with 12-step facilitation therapy, patients who received CBT were significantly more likely to achieve four consecutive weeks of abstinence at the end of the trial compared with subjects assigned to 12-step facilitation (*19*). In another trial, cocaine-dependent subjects were randomly assigned to coping skills training (a CBT-based intervention) or to a meditation and relaxation training control treatment. No difference was seen between groups in the proportion that remained abstinent during the 3-month posttreatment follow-up period, but subjects receiving CBT showed significantly fewer days of cocaine use compared with subjects randomized to the control treatment during the period (*20*).

CBT may be a particularly valuable intervention because cocaine-dependent patients treated with CBT often continue to improve after therapy is complete. As an example, a 1-year follow-up study of patients with a *DSM-IV* diagnosis of cocaine abuse who had been randomized to receive 12 weeks of treatment with CBT, a psychotherapy control treatment, or the antidepressant desipramine found that patients originally assigned to receive CBT continued to improve during the follow-up phase of the trial, whereas patients assigned to the other two treatment groups did not (*21*). In another trial of CBT for CUD, Rawson *et al.* (*11*) found that subjects treated with CBT continued to show improvements in reductions of cocaine use at 26- and 53-week follow-ups (*11*). The continuing positive effects of CBT during the follow-up phase was attributed to the continued application of coping skills taught to the patients during the active phase of treatment.

Both CBT and standard drug treatment require a great deal of infrastructure support for treatment providers, and transportation to the treatment site may also be difficult for some patients. Using therapists trained in CBT may be difficult for many programs. A computer-based CBT treatment program that could be used at the treatment program site, or eventually be converted to a web-based program accessible to patients from home, would help overcome the obstacles inherent in providing treatment in traditional brick-and-mortar treatment facilities. At least one computerized version of CBT has been shown to be effective for the treatment of CUD. For instance, Carroll and Onken (*22*) have developed a computer-based CBT4CBT (computer-based training for CBT) system. In a preliminary trial, 77 subjects seeking outpatient treatment for a range of substance use disorders were randomly assigned to CBT4CBT plus standard addiction treatment or to standard treatment alone (*22*). Participants were alcohol, cocaine, marijuana, or opioid dependent, with the use of multiple substances reported by 80% of participants. At the end of the 8-week trial, participants assigned to the CBT4CBT treatment submitted significantly more urine specimens that were negative for any type of drugs and tended to have longer continuous periods of abstinence during treatment. A 6-month follow-up indicated significantly better durability of effects of CBT4CBT over standard treatment, for both self-report and urine drug screen data (*23*).

A large network meta-analysis of psychosocial treatments for CUD or amphetamine use disorder was recently completed, based on 50 studies including 6942 individuals randomly assigned to 12 different psychosocial interventions compared to another intervention

or treatment as usual (TAU). Studies of CBT, CM, community reinforcement approach, meditation-based therapies, noncontingent rewards, supportive-expressive psychodynamic therapy, 12-step programs, and their combinations were all included in this analysis. Monitored outcomes included abstinence from cocaine or amphetamine by self-report and by urine drug screens at the end of treatment and at 12 weeks and duration of treatment retention. CM or CM combined with either community reinforcement approach or CBT had superior efficacy and acceptability compared to TAU (*24*).

PHARMACOTHERAPY

Despite many years of research, there are, to date, no pharmacotherapies approved for the treatment of CUD. The search nevertheless continues, primarily because CUD is a devastating illness, and psychosocial treatments, although effective for some, have been shown to be ineffective for many other patients with CUD. Recent advances in understanding the neurobiology of CUD have stimulated exploration of several promising pharmacotherapeutic strategies, and several medications have shown potential efficacy in controlled clinical trials. The most promising pharmacological classes thus far include dopamine agonists, such as long-acting amphetamine and modafinil, and GABA agonists/glutamate antagonists, such as topiramate. In addition, some combinations of pharmacological agents (for instance, amphetamine and topiramate) may also be useful.

Dopamine agonists

Agonist treatments have been used successfully to treat both opioid and tobacco use disorders (*25*–*27*). Ideally, in agonist treatment, the medication chosen should be one that activates the same receptor as the abused drug, thus exerting similar effects but with pharmacological properties that render it less abusable than the abused drug. Generally, drugs that enter the brain more slowly, have longer duration of action, or are partial agonists rather than full agonists tend to have less addictive potential. These drugs may be effective treatment for several forms of substance use disorder. Both methadone, because of its slow onset of action, and buprenorphine, by virtue of its partial agonist activity at the opioid receptors, are effective agonist treatments for opioid use disorder. Likewise, the slow absorption of transdermal nicotine and the partial agonist effects of varenicline at the nicotinic acetyl choline receptor are features that contribute to the effectiveness of these drugs for the treatment of tobacco use disorder. A special challenge for pharmacotherapeutic treatments for CUD is the fact that cocaine has diverse effects in the brain, involving multiple kinds of neurotransmitters. Thus, unlike treatment of nicotine and opiate disorders, effective agonists for CUD must be directed toward more than one molecular target.

Three trials of long-acting amphetamine have been conducted thus far, with promising results. The first two trials (*28*, *29*) were conducted by Grabowski *et al.* at the University of Texas. The earliest, 12-week clinical trial (*28*) involved 128 patients with *DSM-IV* cocaine dependence who were randomly assigned to placebo, low-dose dextroamphetamine (30 mg daily), or high-dose dextroamphetamine (60 mg daily). Treatment retention was better in the low-dose amphetamine group. Cocaine use was lower in the high-dose amphetamine group, but the difference was not statistically significant. Dropout rates were high for all groups (*28*). In a subsequent study by the same laboratory (*29*), 120 patients with combined *DSM-IV* cocaine and opioid dependence stabilized on methadone were recruited for a 24-week trial. These patients were randomly assigned to long-acting dextroamphetamine starting at 15 mg daily and increasing to 30 mg daily, long-acting dextroamphetamine from 30 mg daily increasing to 60 mg daily, or placebo treatment. Significant reductions in cocaine use were seen in patients treated with 30/60 mg of dextroamphetamine compared with placebo or 15/30 mg of dextroamphetamine (*29*). Treatment retention was poor in all groups, with fewer than 50% of the subjects completing the trial. In a more recent trial conducted in the Netherlands (*30*), 73 patients with treatment-refractory heroin and cocaine dependence were randomly assigned to receive either 12 weeks of oral sustained-release dexamphetamine (60 mg/day) or a placebo. Both groups received methadone and diacetylmorphine (heroin-assisted treatment) (*30*). Treatment retention was good, with 89% of participants completing the trial. Sustained-release dexamphetamine–treated subjects reported, on average, fewer days of cocaine use compared with placebo-treated subjects (45 days versus 61 days). In addition, dextroamphetamine-treated subjects were more likely to be abstinent for three consecutive weeks compared to those receiving placebo. No serious adverse events occurred in dexamphetamine-treated subjects.

A trial of long-acting amphetamine was also conducted in cocaine-dependent patients with comorbid attention deficit hyperactivity disorder (ADHD) (*31*). In this 13-week trial, 126 subjects who met *DSM-IV-Text Revision* criteria for both ADHD and CUD were randomly assigned to mixed amphetamine salts extended-release (MAS-ER; 60 or 80 mg daily) or to placebo. All subjects also participated in weekly individual CBT. More of the subjects in the two medication groups achieved at least a 30% reduction in ADHD symptom severity compared to the placebo group (75% in the 60-mg group, 58% in the 80-mg group, and 40% in the placebo group). The odds of a cocaine-negative week were significantly higher in the 80-mg group and 60-mg group compared with placebo. Rates of continuous abstinence in the last 3 weeks of the trial were greater for the medication groups than the placebo group: 30% for the 80-mg group and 18% for the 60-mg group versus 7% for the placebo group. Thus, long-acting amphetamine has shown efficacy for the treatment of CUD in cocaine-dependent patients without comorbid psychiatric illness and in cocaine-dependent patients with comorbid ADHD.

Long-acting methamphetamine has also been evaluated for use in treatment of CUD. Mooney *et al.* (*32*) conducted an 8-week trial involving 82 individuals with *DSM-IV* cocaine dependence. Subjects received treatment with sustained-release methamphetamine (30 mg daily), immediate-release methamphetamine (30 mg daily), or placebo. Subjects who received sustained-release methamphetamine submitted fewer cocaine-positive urine drug screens during the trial compared to subjects who received the immediate-release methamphetamine or placebo (29% versus 66% and 60%). Although only 32% of the subjects completed the trial, the retention rate was equally poor in both medicated and control groups. Because this was a proof-of-concept trial, the investigators applied stringent retention criteria, requiring participants to provide at least 75% of the requested data for any 2-week period of the trial. Therefore, failing to attend two visits in a given week would, in most cases, result in the subject being discontinued from the study (*32*).

In most, but not all, trials of long-acting amphetamine or methamphetamine treatment, retention has been poor. In at least one trial, the poor retention rate was due, not to poor tolerability of the medication, but rather to the stringent retention criteria used in

these preliminary proof-of-concept trials. Before long-acting amphetamine or methamphetamine is used clinically, these preliminary trials will need to be replicated in larger trials, using a more standard patient population. However, based on the promise of these trials, other dopamine agonists, including modafinil, have been evaluated for CUD.

Modafinil is a mild stimulant used to treat narcolepsy and shift-work sleep disorder. Modafinil has been shown to increase dopaminergic neurotransmission by blocking the dopamine transporter (*33*). Modafinil also enhances glutamate neurotransmission (*34*). It may be efficacious for CUD either by increasing dopamine transmission or by ameliorating the glutamate depletion seen in chronic cocaine users (*35*).

Modafinil was found to block the euphoric effects of cocaine in several human laboratory studies (*36*–*39*). First, Dackis *et al.* (*36*) conducted a double-blind, placebo-controlled cocaine/modafinil interaction trial. This trial was intended to demonstrate the safety of modafinil for the treatment of CUD and to provide preliminary evidence of possible efficacy. In this trial, cocaine-dependent subjects were given modafinil in 200- or 400-mg doses or a placebo for several days and then challenged with 30 mg of intravenous cocaine on an inpatient research ward. Pretreatment with modafinil significantly blunted cocaine-induced euphoria as measured by scores on the Addiction Research Center Inventory Amphetamine Scale. In a separate, but very similar, human laboratory trial, Malcolm *et al.* (*37*) found that modafinil administered at both 400- and 800-mg doses significantly reduced visual analog scale ratings of "high," "any drug effect," and "worth in dollars" compared to cocaine alone. Hart *et al.* (*38*) evaluated the effect of modafinil on the self-administration of cocaine in a human laboratory trial. In this trial, the effects of modafinil maintenance (0, 200, and 400 mg/day) on subjects' responses to smoked cocaine (0, 12, 25, and 50 mg) were examined in eight non–treatment-seeking cocaine-dependent individuals. Higher cocaine doses significantly increased cocaine self-administration, cocaine subjective-effect ratings, and cardiovascular measures. Modafinil at both 200 and 400 mg daily markedly attenuated these effects. More recently, Verrico *et al.* (*39*) evaluated modafinil and the combination of modafinil and the antidepressant escitalopram in a human laboratory trial. Forty eight *DSM-IV* non–treatment-seeking cocaine-dependent subjects were randomized to modafinil (200 mg/day), escitalopram (20 mg/day), or modafinil + escitalopram (200 + 20 mg/day) for 5 days. On day 5, during separate sessions, participants received an intravenous sample of 20 mg of cocaine. Compared to placebo, modafinil pretreatment was associated with significant reductions in ratings of "any drug effect," "high," "stimulated," and "good effect" associated with cocaine administration. The addition of escitalopram did not enhance the efficacy of modafinil to reduce any of the measures noted above.

Based in part on these very positive human laboratory trials, modafinil was evaluated in several clinical trials but with only mixed results. Some of the differences in trial outcome may be explained by comorbid alcohol abuse among some of the subjects. Some of the differences may also be explained by the severity of CUD in the sample being tested or by varying adherence to modafinil treatment.

The first clinical trial of modafinil was conducted with a sample of 62 individuals with *DSM-IV* cocaine dependence treated for 8 weeks. In that trial, modafinil-treated subjects (400 mg daily) submitted significantly more cocaine metabolite-free urine samples compared with placebo-treated patients (42% versus 22%) and were rated as more improved compared with placebo-treated patients (*40*). This trial was followed by a 12-week multicenter trial in which 210 subjects with *DSM-IV* cocaine dependence were randomly assigned to receive modafinil 200 mg daily or placebo. No difference was found in cocaine use outcomes between the two groups. In a post hoc analysis among patients who were not concurrently alcohol dependent, modafinil increased abstinence from cocaine compared with placebo (*41*). In an 8-week trial with 94 cocaine-dependent individuals without comorbid alcohol dependence, Kampman *et al.* (*42*) found that subjects treated with modafinil were significantly more likely to be abstinent from cocaine during the last 3 weeks of the trial compared with subjects receiving placebo (23% versus 9%).

Two other large trials of modafinil produced negative results. In one trial, 210 *DSM-IV* cocaine-dependent subjects without comorbid alcohol dependence participated in an 8-week clinical trial comparing modafinil (200 or 400 mg/day) with placebo. There was no significant difference in cocaine use or cocaine craving among the test groups (*43*). The failure to find an effect of modafinil may be attributed to the selection of subjects, all of whom tested positive for cocaine at baseline. It is well established that cocaine-dependent subjects who test positive for cocaine at the start of the study have extremely poor clinical outcomes when compared to those who are able to produce a cocaine-negative urine sample (*44*–*47*). More recently, 65 crack cocaine–dependent outpatients were randomized to receive either 12-week individual CBT plus modafinil (400 mg/day) or 12-week individual CBT only. Modafinil adherence was low, with only 10% of subjects completing treatment. Intent-to-treat analyses showed that modafinil did not improve CBT treatment retention or any of the cocaine-related outcomes. Both groups showed similar, large reductions in cocaine use during the trial. Post hoc exploratory analyses within the CBT plus modafinil group showed significantly larger baseline to week 12 reductions in cocaine use days in subjects who took modafinil for more than 8 weeks (*48*).

Overall, the mixed results of modafinil trials to date do not suggest significant efficacy of this drug in cocaine users as a whole. However, modafinil has shown efficacy in certain subpopulations of cocaine users, in particular those without comorbid alcohol use. The efficacy of modafinil may also be sensitive to degree of adherence to treatment. In most trials, modafinil has been shown to be well tolerated and it has low abuse liability, making it a potentially safer choice of dopamine agonist for the treatment of CUD.

GABAergic/glutamatergic medications

Mesocortical dopaminergic neurons receive modulatory inputs from both GABAergic and glutamatergic neurons. As GABA is primarily an inhibitory neurotransmitter in the central nervous system, activation of GABAergic neurons tends to decrease activity in the dopaminergic reward system. Preclinical trials of medications that foster GABAergic neurotransmission have suggested that these compounds reduce the dopamine response to cocaine administration and to conditioned reminders of prior cocaine use (*49*–*51*). GABAergic medications also reduce the self-administration of cocaine in animal models (*52*, *53*), suggesting that GABAergic medications could prevent relapse by blocking cocaine-induced euphoria or by reducing craving caused by exposure to conditioned reminders of prior cocaine use. Animal studies of cocaine-induced neuroplasticity have demonstrated that changes in glutamate transmission in the nucleus accumbens are important for the development and expression of the neuroadaptations thought to underlie cocaine addiction (*54*). Medications

that block glutamatergic input into the nucleus accumbens could reduce cocaine craving and prevent relapse to cocaine use in cocaine-dependent individuals (*55*).

The GABA agonist/glutamate antagonist topiramate has effects on both GABA neurotransmission and glutamate neurotransmission and therefore may be an effective anti-relapse medication. Topiramate increases cerebral levels of GABA and facilitates GABA neurotransmission (*56*, *57*). Topiramate also inhibits glutamate neurotransmission through a blockade of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid)/kainate receptors (*58*). In animal models of cocaine relapse, blockade of AMPA receptors in the nucleus accumbens prevented reinstatement of cocaine self-administration (*59*).

To test the potential of topiramate for the treatment of CUD, our laboratory (*60*) carried out a pilot study involving 40 subjects with *DSM-IV* cocaine dependence, treated for a period of 13 weeks. Subjects were randomly assigned to topiramate (200 mg) daily or to placebo. Topiramate-treated subjects showed a significantly higher rate of abstinence during the last 5 weeks of the trial compared to placebo-treated patients. Among patients who returned for at least one visit after receiving medications, topiramate-treated subjects were also significantly more likely to achieve at least 3 weeks of continuous abstinence from cocaine compared to placebo-treated patients (59% versus 26%), and topiramate-treated subjects were significantly more likely than placebo-treated subjects to be rated very much improved at their last visit (71% versus 32%) (*60*).

Later work has confirmed and expanded upon these initial results. In a second, larger 13-week trial in our laboratory (*61*), involving 170 cocaine- and alcohol-dependent subjects, topiramate-treated subjects (300 mg daily) were significantly more likely to achieve 3 weeks of continuous abstinence from cocaine at the end of the trial. Twenty percent of the topiramate-treated patients were cocaine abstinent compared to 6% of the placebo-treated patients. Johnson *et al.* (*62*) also evaluated the efficacy of topiramate in 142 cocaine-dependent subjects in a 12-week double-blind, placebo-controlled trial. In that trial, topiramate-treated subjects had significantly more cocaine nonuse days than placebo-treated subjects during weeks 6 to 12 of the trial. Cocaine nonuse days were determined by self-reporting, verified by urine drug screens. In a third trial (*63*) involving 60 men dependent on crack cocaine, topiramate was found to reduce cocaine use early in treatment. Subjects were randomly assigned either to topiramate, up to 200 mg daily titrated over several weeks, or to a placebo. During the first 4 weeks of the trial, topiramate-treated subjects used significantly less cocaine measured by quantity used and frequency of use. The subjects also spent significantly less money on cocaine during that time. However, at the conclusion of the 12-week trial, there were no significant differences between topiramate and placebo-treated subjects in any outcome variable. The studied groups did not differ with regard to secondary end points, such as study dropout and the number of subjects who reported side effects (*63*).

Three negative trials of topiramate have also been published. Two of these studies involved patients with CUD and comorbid opioid use disorder, and in the third trial, involving subjects with CUD alone, adherence to topiramate was poor. In the first trial, Umbricht *et al.* (*64*) evaluated the efficacy of topiramate and CM in 171 *DSM-IV* cocaine- and opioid-dependent subjects receiving methadone maintenance. Subjects were randomly assigned to one of four groups. Under a factorial design, participants received either topiramate or placebo, and monetary voucher incentives that were either contingent (CM) or non-contingent (Non-CM) on drug abstinence. Topiramate-treated subjects were inducted onto topiramate over 7 weeks, stabilized for 8 weeks at 300 mg daily, and then tapered over 3 weeks. Voucher incentives were supplied for 12 weeks, starting from the fourth week of topiramate induction. Primary outcome measures were cocaine abstinence and treatment retention. In this trial, neither topiramate nor CM was effective in reducing cocaine use. There was no significant difference in cocaine abstinence between the topiramate and placebo-treated groups or between the CM-treated and the non–CM-treated groups. There was no significant topiramate/CM interaction. Retention was not significantly different between the groups (*64*). In another negative trial of topiramate in comorbid cocaine- and opiate-dependent patients (*65*), 50 cocaine-dependent individuals maintained on methadone were randomized to receive topiramate up to 300 mg daily or identical placebo capsules. In addition, all subjects received brief behavioral compliance enhancement treatment (BBCET). Primary outcome measures included cocaine abstinence, verified by urine drug screens, and treatment retention. Topiramate was well tolerated but not better than placebo in reducing cocaine use (*65*). In the third trial, Nuijten *et al.* (*66*) conducted a trial of topiramate involving 74 crack cocaine–dependent outpatients. The subjects were randomized to receive either 12-week CBT plus topiramate staring at 25 mg daily and rapidly titrated over 3 weeks to 200 mg daily or 12-week CBT only. The primary outcome measure was treatment retention. Secondary outcomes included medication adherence, safety, cocaine and other substance use, health, social functioning, and patient satisfaction. Adherence to topiramate treatment was low. In the intent-to-treat analyses, topiramate neither improved treatment retention nor reduced cocaine and other substance use (*66*).

Combinations of topiramate and long-acting amphetamine

On the basis of the positive trials of long-acting dopamine agonists for CUD and the positive trials of topiramate for CUD, Mariani *et al.* (*67*) evaluated the combination of topiramate and mixed amphetamine salts for the treatment of CUD. Eighty-one cocaine-dependent adults were randomized to receive a combination of MAS-ER and topiramate or placebo for 12 weeks. MAS-ER doses were titrated over 2 weeks to a maximum dose of 60 mg daily, and topiramate doses were titrated over 6 weeks to a maximum dose of 300 mg daily. All participants received a supportive behavioral intervention. The overall proportion of subjects who achieved three consecutive weeks of abstinence was larger in the MAS-ER and topiramate group (33.3%) than in the placebo group (16.7%). There was a significant moderating effect of baseline total number of cocaine use days on outcome, suggesting that the combination treatment was most effective for participants with a high baseline frequency of cocaine use (*67*).

In short, there is mixed evidence for the efficacy of topiramate in treatment of CUD. Comorbid opioid use disorder was associated with negative results in two trials. In a third trial, topiramate was poorly tolerated. However, in this trial, topiramate was rapidly titrated to 200 mg daily in 3 weeks, which is faster than the dose titration in other trials, and this may have contributed to its poor tolerance (*66*).

Cholinergic medications

Galantamine is a reversible and competitive inhibitor of acetylcholinesterase that increases synaptic concentrations of acetylcholine, resulting in stimulation of both nicotinic and muscarinic receptors. Evidence suggests that disruptions in the cholinergic system are

associated with cocaine use (*68*). Thus, galantamine might be useful as a treatment for CUD.

There have been two positive trials of galantamine to date. In a small pilot trial (*69*), galantamine was well tolerated and associated with reductions in cocaine use in subjects with CUD. Subsequently, the same laboratory conducted a larger trial testing galantamine for 120 patients with comorbid CUD and OUD stabilized on methadone maintenance. In this trial, galantamine (8 mg daily) plus computerized CBT was found to be superior to standard treatment in reducing the frequency of cocaine use (*70*). These interesting preliminary results warrant further investigation.

DISCUSSION

Pharmacotherapy for CUD is still limited; no medication has yet been approved for the treatment of CUD. The most consistent positive results in clinical trials of potential medications have been obtained with long-acting stimulants, including long-acting dextroamphetamine and long-acting mixed amphetamine salts. There have been several positive trials of topiramate for CUD, although there have been several trials that yield negative results as well. Topiramate efficacy has not been shown in patients with comorbid OUD. Topiramate also has side effects that may make it difficult to tolerate fatigue and general mental slowing (*61*, *62*, *66*). Combinations of topiramate and long-acting stimulants take advantage of two separate mechanism of action and thus far seem to offer benefits over stimulants or topiramate alone. Replication trials are needed.

Several issues in the development of medications for CUD still need to be addressed. First, it should be kept in mind that CUD is a heterogeneous disorder and that this heterogeneity may be affecting results in pharmacotherapy trials. Identifying subgroups of patients with SUD and targeting medications to these subgroups may improve our ability to identify effective medications. Medications currently showing potential efficacy such as topiramate and long-acting amphetamines have some safety and tolerability issues that need to be addressed. Identifying long-acting dopamine agonists or partial agonists that are safe and well tolerated would make this treatment strategy more applicable to treatment in clinics. Likewise, GABA/glutamatergic medications such as topiramate but without the associated cognitive side effects should be pursued. Last, identifying new strategies such as cholinergic medications is welcome.

In contrast to pharmacotherapy, there are several forms of psychosocial treatment for CUD that have been proven to be beneficial. The most robust of these treatments is CM in the form of VBRT. This behavioral treatment has been shown to be effective generally as an augmenting agent to other forms of psychosocial treatment. Regardless of the base psychosocial treatment, the addition of CM has been shown to improve outcomes. CM remains the most reliable method of converting an actively using patient with CUD to a newly abstinent patient with CUD.

Challenges confronting the development of psychosocial treatments for CUD lie less in identifying more effective strategies but more on finding innovative ways of applying these strategies. CM is effective but can be costly and inconvenient. Finding innovative ways to reward abstinence among cocaine users is a challenge. Identifying ways to sustain the benefits of CM over longer periods of time is a challenge. Other challenges include identifying innovative platforms for providing psychosocial treatment. Taking advantage of new technologies and transferring the site of treatment from the clinic to patients' residences, where condition reminders of prior drug use provoke craving, are research priorities.

REFERENCES AND NOTES

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