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Psychostimulant addiction treatment

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Abstract

Treatment of psychostimulant addiction has been a major, and not fully met, challenge. For opioid addiction, there is strong evidence for the effectiveness of several medications. For psychostimulants, there is no corresponding form of agonist maintenance that has met criteria for regulatory approval or generally accepted use. Stimulant-use disorders remain prevalent and can result in both short-term and long-term adverse consequences. The mainstay of treatment remains behavioral interventions. In this paper, we discuss those interventions and some promising candidates in the search for pharmacological interventions.

Introduction

Treatment of psychostimulant¹ addiction has been a major, and not fully met, challenge. For opioid addiction, there is strong evidence for the effectiveness of several medications, including methadone, buprenorphine, and naltrexone. For psychostimulants, there is no corresponding maintenance medication that has met criteria for regulatory approval or generally accepted use. The mainstay of treatment has been behavioral interventions such as cognitive-behavioral therapy (CBT). In this paper, we will discuss advances in pharmacological as well as behavioral treatments for psychostimulant addiction.

The epidemiology of psychostimulant addiction has been discussed in detail by Henningfield et al. in this issue. Suffice it to say that psychostimulant-use disorders are a major public-health problem in both the United States and globally. In the 2010 National Survey on Drug Use and Health, 357,000 adults aged 12 or older reported past-year amphetamine dependence or abuse and about 1 million reported past-year cocaine abuse or dependence. Among persons aged 12 or over, 343,000 individuals had most recently received past-year treatment for amphetamine-related problems and 699,000 had most recently received past-year treatment for cocaine-related problems (Substance Abuse and Mental Health Services Administration, 2011). In 2010, the global annual prevalence (and

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¹We define “psychostimulant” to include agents that act primarily by increasing synaptic levels of dopamine and other monoamines. We use the more precise term “psychostimulant” rather than “stimulant” except when we refer to DSM-defined Stimulant-Use Disorder. We also use DSM-5-consistent terms such as “cocaine-use disorder” when describing the conditions targeted in the clinical trials we cite, though most of the trials cited actually used DSM-IV “dependence” as their enrollment criterion.

number) of illicit drug users was 0.3–1.2 percent (14.3–52.5 million) for amphetamine-type psychostimulants, excluding MDMA, and 0.3–0.4 percent (13.2–19.5 million) for cocaine (United Nations Office on Drugs and Crime, 2012).

One trend that has attracted particular attention during the past ten years or so has been the use of nonprescribed amphetamines or methylphenidate as a study aid among college students (Arria & DuPont, 2010). This trend is only the most recent manifestation of a history of such use that dates back to 1936, when preadolescent students began referring to amphetamine tablets (prescribed to them for post-lumbar-puncture headaches) as “math pills” (Bradley, 1937; Gross, 1995) and University of Minnesota students (in a clinical trial of amphetamine for the common cold) began to use amphetamine for all-night study sessions (Rasmussen, 2006). Still, the wide availability of prescribed and diverted methylphenidate and amphetamines among college students is a cause for concern (Arria & DuPont, 2010).

Overview of psychostimulant pharmacokinetics and pharmacodynamics

The pharmacokinetics and pharmacodynamics of psychostimulants are discussed elsewhere in this issue. In brief, methamphetamine is structurally very similar to amphetamine and related agents, such as MDMA (3,4-methylenedioxy-*N*-methylamphetamine), which is widely known as “ecstasy,” and designer drugs, such as cathinone derivatives (including “bath salts”). The amphetamines, including methamphetamine, are similar to cocaine in causing an increase in synaptic levels of the monoamine neurotransmitters dopamine (DA), norepinephrine (NE), and serotonin, in both the central nervous system (CNS) and peripheral nervous system (PNS) (Lott, Kim, Cook, & de Wit, 2006; Rothman et al., 2000; White & Kalivas, 1998). Cocaine is a reuptake inhibitor; amphetamines are releasers, taken up by the reuptake transporter in exchange for neurotransmitter (Koob & Bloom, 1988).

Cocaine is sold in a variety of forms, including hydrochloride salt, sulfate, and a base (either freebase, or crystallized as crack) (*Clinical Textbook of Addictive Disorders*, 2005). Hydrochloride salt is an acidic, water-soluble powder with a high melting point, often “cut” with other substances that either add bulk or simulate cocaine’s effect to increase profit (Shesser, Jotte, & Olshaker, 1991). The hydrochloride salt does not readily vaporize like the freebase, so it is most often dissolved in water and injected intravenously, or snorted or sniffed through the nose. Intranasally, the bioavailability of cocaine is about 60% (Barnett, Hawks, & Resnick, 1981). Cocaine sulfate (“paste”) can be smoked in tobacco, but due to its melting point of almost 200°C, this is inefficient. Cocaine freebase is made by adding a strong base to an aqueous solution of cocaine and extracting the alkaline freebase precipitate. It has a melting point of 98°C and can be vaporized for inhalation. Crystallized forms of freebase cocaine are sold as crack or rock. Smokable cocaine in any form can produce an especially rapid onset of an intense high, which increases its addictive potential (Jenkins, Keenan, Henningfield, & Cone, 2002). Regardless of form or route, the effect of cocaine on the brain and target organs is the same (Hatsukami & Fischman, 1996).

Methamphetamine has two differentially active stereoisomers. The L-enantiomer has peripheral alpha-adrenergic activity and has been used as a nasal decongestant. The D-

enantiomer is a powerful stimulant with 3–5 times the CNS activity of the L-enantiomer. It can be insufflated, smoked, injected, or taken orally or per rectum and is highly lipophilic, so it enters the brain faster than other psychostimulants (including amphetamine) and is less vulnerable to enzymatic degradation in the brain; its half-life is 10–12 hours (Cruickshank & Dyer, 2009; Schep, Slaughter, & Beasley, 2010). Methamphetamine is more potent and more efficacious than amphetamine, producing much higher concentrations of synaptic dopamine (Goodwin et al., 2009) and more toxic effects on nerve terminals (Carvalho et al., 2012; Volkow et al., 2001; Yamamoto, Moszczynska, & Gudelsky, 2010). Given its pharmacokinetics and low cost, methamphetamine tends to be self-administered chronically and continuously in high doses when used in nonmedical contexts (Winger, Woods, & Hofmann, 2004).

Some psychostimulants, including methylphenidate, amphetamine, and methamphetamine are approved in the US for treatment of Attention Deficit Hyperactivity Disorder (ADHD) (Dopheide & Pliszka, 2009), weight control (Greenway & Caruso, 2005), and narcolepsy (Morgenthaler et al., 2007). Given their abuse potential, diversion can and does occur (Sembower, Ertischek, Buchholtz, Dasgupta, & Schnoll, 2013; Sweeney, Sembower, Ertischek, Shiffman, & Schnoll, 2013). Some psychostimulants have been removed from the US market due to specific forms of toxicity. For example, use of phenylpropanolamine, which was used primarily for weight control, was found to be related to hemorrhagic stroke in women and removed from the market in 2005.

Cathinone is an alkaloid psychostimulant found in the *khât* (*Catha edulis*) plant, which grows at high altitudes in East African and the Middle East (Al'Absi & Grabowski, 2012). Its actions and effects are similar to those of the amphetamines (Kalix, Brenneisen, Koelbing, Fisch, & Mathys, 1991). Like other psychostimulant misusers, *khât* misusers are at increased risk for acute myocardial infarction and stroke due to inotropic and chronotropic effects on the heart, vasospasm of coronary arteries, and catecholamine-induced platelet aggregation (Al Suwaidi, Ali, & Aleryani, 2013). With increasing frequency, *khât* use has been seen in Europe and North America, making it a concern on a global scale.

Clinical Effects of Psychostimulants

Regardless of the route of administration, or even the specific drug used, psychostimulants produce the same basic spectrum of acute CNS effects: euphoria, increased energy/decreased fatigue, reduced need for sleep, decreased appetite, decreased distractibility, increased self-confidence and alertness, increased libido, and prolonged orgasm. Peripheral effects may include tremor, diaphoresis, increased muscle tension, tachypnea, hyperreflexia, and hyperpyrexia (Romanelli & Smith, 2006; Winger et al., 2004). Many of the effects are biphasic; for example, low doses improve psychomotor performance while higher doses may cause tremors or convulsions. Cardiovascular effects (alpha-adrenergically mediated) are also biphasic, with low doses decreasing heart rate via the vagus nerve and high doses causing increased heart rate and vasoconstriction, leading to increased blood pressure. Over several hours, days, or weeks, psychostimulant use can result in restlessness, irritability, and insomnia and at higher doses, suspiciousness, repetitive stereotyped behaviors, and bruxism (Ellinwood & Lee, 1989; Fasano et al., 2008; Romanelli & Smith, 2006). Overdose

manifests predominantly as sympathetic nervous system overactivity, possibly culminating in convulsions, cerebral hemorrhage or infarct (Gay, 1982), cardiac arrhythmias or ischemia (Karch, 2005), respiratory failure (Gay, 1982), or rhabdomyolysis (Roth, Alarcon, Fernandez, Preston, & Bourgoignie, 1988).

Stimulant-Use Disorders and Withdrawal

The Diagnostic and Statistical Manual of Psychiatric Disorders, 5th edition (DSM-5) defines a Stimulant-Use Disorder (SUD) as a pattern of use of amphetamine-type substances, cocaine, or other stimulants leading to clinically significant impairment or distress, as manifested by at least two of the following 11 problems within a 12-month period: taking larger amounts or over a longer period of time than intended; persistent desire or unsuccessful efforts to cut down or control; great deal of time spent in activities necessary to obtain, use, or recover; craving; use resulting in failure to fulfill major role obligations; continued use despite recurrent social or interpersonal problems; giving up social, occupational, or recreational activities; recurrent use in physically hazardous situations; continued use despite persistent or recurrent physical or psychological problems; tolerance; withdrawal symptoms, or avoidance of withdrawal symptoms by continued use (American Psychiatric Association, 2013).²

Withdrawal from psychostimulants often includes hypersomnia, increased appetite, and depressed mood. Acute withdrawal typically lasts 7–10 days, but residual symptoms, possibly associated with neurotoxicity, may persist for several months (Cruikshank & Dyer, 2009). Unlike opioids (and unlike alcohol or sedatives taken daily in large doses), psychostimulants do not generally produce withdrawal of such severity as to be among the main drivers of ongoing use. In fact, there is still some disagreement about the basic phenomenology of psychostimulant withdrawal—such as whether it can be divided into discrete phases in which the symptoms get worse before they get better (Foltin & Fischman, 1997; Gawin & Kleber, 1986) or whether the symptoms decline monotonically (Coffey, Dansky, Carrigan, & Brady, 2000; Weddington et al., 1990). Most current theories of addiction that attempt to account for psychostimulant addiction emphasize the primary role of conditioned craving, which can persist long after physiological withdrawal has abated (Robinson & Berridge, 2008).

Behavioral Treatment

Behavioral therapies, including Cognitive-Behavioral Therapy (CBT), the Community Reinforcement Approach (CRA), contingency management, combinations of these, and others remain the mainstay of treatment for stimulant-use disorders (Carroll, 1996, 1997; Ciccarone, 2011). A meta-analysis of several behavioral therapies for cocaine-use disorder found that they produced modest benefits (Dutra et al., 2008). Another analysis found that the behavioral and psychosocial interventions did not appear have a differential effects as a function of the drug being targeted (cocaine or methamphetamine) (Vocci & Montoya, 2009).

²The DSM stipulates that if the only two criteria met are tolerance and withdrawal, and the drug is being used as medically prescribed, the diagnosis of SUD is not made.

CBT is a time-limited, present-oriented psychotherapy in which the drug-abusing patient is helped to identify the thoughts, feelings, and events that precede and follow each episode of drug use and to develop and rehearse coping skills (Carroll, 2000). Based on social-learning theory, CBT contends that people begin to use and abuse substances mostly because they learn to do so. Mechanisms of such learning include modeling, operant conditioning, and classical conditioning (Carroll, 2000). CBT has two critical components: functional analysis and skills training. Functional analysis includes identifying the patient's thoughts, feelings, and circumstances before and after episodes of psychostimulant use, and skills training helps the patient unlearn old habits associated with psychostimulant abuse and learn or relearn healthier skills and habits (Carroll, 1998). CBT is didactic and structured. A typical structure for a course of CBT is in 8–10 topic-driven weekly 60-minute sessions, each of which includes reviewing practice exercises, debriefing on problems since the last session, skills training, feedback on skills training, in-session practice, and planning for the next week. Sessions are often divided into thirds; the first third concentrates on assessing the patient's status, the second third on introducing and discussing the session topic, and the final third on exploring the patient's understanding of and reactions to the topic (Carroll, 2000). There is evidence that CBT is effective for both cocaine-use disorder (Darker et al., 2012; Maude-Griffin et al., 1998; Rohsenow, Monti, Martin, Michalec, & Abrams, 2000) and methamphetamine-use disorder (Lee & Rawson, 2008), although its benefits might not become fully apparent until up to a year after a 12-week course of treatment has ended (Carroll, 1996), presumably because the consistent expression of the cognitive skills learned will increase over time.

Contingency management is a purely behavioral treatment, conceptually based on operant conditioning. Contingency management reinforces desired behaviors with incentives such as monetary rewards or vouchers for goods and services that are consistent with treatment goals. Randomized controlled trials have demonstrated the effectiveness of contingency management in producing short-term abstinence in patients with cocaine-use disorder (Epstein, Hawkins, Covi, Umbricht, & Preston, 2003; Secades-Villa et al., 2013), dual-diagnosis patients with cocaine addiction and mental-health issues (McDonell et al., 2013; Petry, Alessi, & Rash, 2013), and patients with methamphetamine-use disorder (Roll, Chudzynski, Cameron, Howell, & McPherson, 2013; Roll et al., 2006). Contingency management may improve quality of life in addition to reducing substance abuse (Andrade, Alessi, & Petry, 2012). The effects of combining contingency management with CBT may be complex, as CBT may reduce the immediate benefits of contingency management while improving long-term outcomes (Roll et al., 2006). Combining contingency management with CRA has been more consistently successful (Secades-Villa et al., 2011).

Pharmacological Treatment

Pharmacological interventions for SUDs may include agonist therapy, antagonist therapy (including vaccines, in research settings), and symptomatic relief of withdrawal symptoms or of a comorbid mental or cognitive disorder. The strategy may be to change psychostimulant metabolism, to reduce craving, or to change the balance of reinforcing and aversive effects of psychostimulant self-administration. Numerous pharmacological agents have been tried for SUDs over the years, with limited success. We will discuss some of the

more promising pharmacological agents in detail and provide a brief overview of those with equivocal results. It is important to note that the strongest evidence for or against the efficacy of any treatment comes from double-blind, randomized clinical trials with appropriate negative and/or positive controls and with enough participants to make negative results credible. *Post hoc* findings of benefits in subsets of the original sample, especially in the absence of positive finding on the primary measure, should be viewed with skepticism.

Table 1 shows the design, subject population, primary objectives, and main results of each clinical trial described below.

Naltrexone

Naltrexone hydrochloride (NTX) is a non-selective competitive antagonist at opioid receptors. It reduces alcohol consumption in laboratory animals and reduces the positive subjective effects of alcohol in humans (Setiawan et al., 2011); in clinical trials for treatment of alcoholism, it reduces relapse and to a lesser degree enhances abstinence, both in adolescents (De Sousa & De Sousa, 2008; Deas, May, Randall, Johnson, & Anton, 2005) and adults (Garbutt, 2010). The mechanism of action of NTX in alcoholism is not fully understood, but preclinical data suggest that it may partly involve blockade of the effects of endogenous opioids (Chiu, Ma, & Ho, 2005).

The therapeutic potential of NTX in stimulant-use disorder is supported by findings that it attenuates amphetamine-induced and amphetamine-cue-induced locomotor behavior in laboratory animals (Haggkvist et al., 2011). In mice, NTX also prevented methylphenidate reward (as assessed by conditioned place preference) and methylphenidate-induced mu-opioid-receptor activation (Zhu, Spencer, Liu-Chen, Biederman, & Bhide, 2011). This finding suggests that a naltrexone/methylphenidate combination could have less abuse potential than a methylphenidate monotherapy and could be the basis of agonist maintenance for addiction to other psychostimulants (Zhu et al., 2011).

The salience of the dopaminergic–opioid interaction in the human brain with regard to cocaine abuse was further demonstrated by Gorelick et al. (Gorelick et al., 2005), who showed an increase in μ -opioid receptor binding in some brain regions of individuals diagnosed with cocaine dependence. Blockade of μ -opioid receptors by NTX attenuated the subjective effects of amphetamine in patients with amphetamine-use disorder under double-blind conditions (Jayaram-Lindstrom et al., 2008).

In sum, the evidence supporting the utility of NTX in SUD treatment is building. Its low abuse potential, benign side-effect profile (nausea and vomiting in a small number of patients), and good safety profile (hepatic injury can occur at high doses but not at those currently recommended) point toward it becoming a possible pharmacological agent in the arsenal against SUDs.

Disulfiram/Antabuse

The rationale for using disulfiram in the treatment of cocaine-use disorder is that it inhibits the norepinephrine-synthesizing enzyme dopamine-beta-hydroxylase (DBH), increasing the brain ratio of dopamine to norepinephrine, and that it stimulates dopamine release from

noradrenergic terminals (Devoto, Flore, Saba, Cadeddu, & Gessa, 2012). Initial placebo-controlled human studies have supported the efficacy of disulfiram for treatment of cocaine-use disorder in buprenorphine-maintained polydrug users (George et al., 2000) and in cocaine-only users (Carroll et al., 2004). However, more recent evidence in methadone-maintained patients is less promising (Carroll, Nich, Shi, Eagan, & Ball, 2012; Oliveto et al., 2011). Disulfiram may be effective for treatment of cocaine addiction only in individuals with the genotype for normal levels of DBH (Kosten et al., 2013). There is also evidence that genotypes for ANKK1, DRD2, or both, may be used to identify cocaine users for whom disulfiram may be effective (Spellicy, Kosten, Hamon, Harding, & Nielsen, 2013). The effectiveness of disulfiram may also be greater for men than for women (Nich et al., 2004).

Agonist-like replacement therapy

The rationale behind agonist-like replacement therapy in the treatment of SUDs is that a low-dose, slow-release psychostimulant formulation should alleviate craving and block the euphorigenic effects of cocaine or methamphetamine while having little or no abuse potential of its own. Given the nonselective monoaminergic actions of cocaine and methamphetamine, possible targets include the dopamine (DA), serotonin (5-HT), and norepinephrine (NE) systems (Herin, Rush, & Grabowski, 2010).

Preclinical research has supported the use of d-amphetamine itself as an agonist-like medication (Mello & Negus, 2007; Negus & Mello, 2003). Early clinical studies showed that d-amphetamine improved retention in treatment and reduced illicit cocaine use (Grabowski et al., 2001). Galloway et al. (Galloway et al., 2011) conducted a randomized, placebo-controlled, double-blind clinical trial of oral d-amphetamine in treatment-seeking individuals with methamphetamine-use disorder and found that while d-amphetamine did not reduce methamphetamine use, it did reduce withdrawal symptoms and craving.

Another potential maintenance agent is sustained-release methamphetamine. Mooney et al. (Mooney et al., 2009) tested it as a treatment for cocaine-use disorder in a randomized, double-blind, placebo-controlled study and found that it was well-tolerated and that it reduced cocaine craving and rates of cocaine-positive urine samples.

Methylphenidate, a psychostimulant that acts by inhibiting reuptake of DA (and, to a lesser degree, 5-HT and NE) (Bymaster et al., 2002), initially was not shown to be superior to placebo for treatment of cocaine-use disorder (Grabowski et al., 1997). More recent studies are equivocal on whether there is a role for methylphenidate in treatment of amphetamine-use disorder (Miles et al., 2013; Zhu et al., 2011).

Modafinil, a marketed stimulant with multiple mechanisms of action, was initially found to decrease cocaine euphoria in a human laboratory study (Dackis et al., 2003). However, more recent clinical trials in patients with cocaine-use disorder (Dackis et al., 2012) or methamphetamine-use disorder (Anderson et al., 2012; Shearer et al., 2009) have been equivocal, as have studies of a combination of d-amphetamine and modafinil (Schmitz et al., 2012). The post-hoc findings from these studies suggest that modafinil may be more efficacious in less severe cases of addiction. Modafinil's properties as a cognitive enhancer might address the cognitive impairments in attention, working memory, and response-

inhibition functions seen in chronic psychostimulant misusers (Mereu, Bonci, Newman, & Tanda, 2013; Sofuoglu, DeVito, Waters, & Carroll, 2013).

One group of investigators, drawing on their clinical and epidemiological experience in South America, has argued persuasively that coca tea consumed as a beverage does not lead to maladaptive patterns of use (at least, no more than coffee does) and that oral coca shows promise as an agonist replacement treatment for cocaine addiction (Llosa & Llosa, 2005). We speculate that the relative lack of follow-up on this line of research may have more to do with political, cultural, and commercial considerations than with scientific ones.

Other medications

There is little evidence for the efficacy of direct DA-receptor agonists (bromocriptine, pergolide), MAO-B inhibitors (selegiline), or certain other dopaminergic drugs (such as amantadine) in SUDs (Soares, Lima, Reisser, & Farrell, 2003).

Antidepressants have been extensively tested for treatment of SUDs, given they have generally acceptable side-effect profiles, good compliance rates, and low abuse potential, and that they may counter some of the long-term effects of psychostimulants on catecholamine receptors (Lima, Reisser, Soares, & Farrell, 2003). Desipramine, bupropion, and fluoxetine seemed promising in initial studies of SUDs, but follow-up studies have been less convincing (Pani, Trogu, Vecchi, & Amato, 2011).

Bupropion is used for depression and smoking cessation; its actions include inhibition of the DA transporter. Human laboratory studies with bupropion have been equivocal (Oliveto et al., 2001; Stoops, Lile, Glaser, Hays, & Rush, 2012). In a double-blind, placebo-controlled, multicenter study, Elkashef et al. (Elkashef et al., 2008) found that bupropion had no overall effect on illicit methamphetamine use in addicted individuals, but that it did (in one of several subgroup analyses specified *a priori*) reduce use among male patients who had a lower level of methamphetamine use at baseline. There was no differential effect as a function of comorbid ADHD or depression.

Aripiprazole, a second-generation antipsychotic drug also used in the treatment of depression, has shown no efficacy in clinical trials of cocaine-use disorder (Sabioni, Ramos, & Galduroz, 2013) or methamphetamine-use disorder (Coffin et al., 2013; Sulaiman et al., 2013).

Mirtazapine, an antidepressant with sedative and anxiolytic properties, did not facilitate retention or recruitment in outpatient treatment for methamphetamine withdrawal, although the authors noted that their study may have been underpowered (Cruickshank et al., 2008).

Doxazosin, an alpha-adrenergic antagonist marketed as an antihypertensive, may reduce cocaine use in people seeking treatment for cocaine-use disorder (Newton et al., 2012). In a 13-week, placebo-controlled study by Shorter et al. (Shorter, Lindsay, & Kosten, 2013), doxazosin titrated over weeks to a dose of 8mg/day resulted in a greater total number of cocaine-negative urines, percentage of total cocaine-negative urines by group, and

percentage of participants achieving 2 or more weeks of cocaine abstinence when compared to placebo.

GABAergic agonists, including baclofen, tiagabine, topiramate, and vigabatrin (Minozzi et al., 2008), have met with only limited success in treating SUDs, as have a variety of other agents, including amantadine, carbamazepine (Lima, Lima, Soares, & Farrell, 2002), and buprenorphine (Gardner & Kosten, 2007).

Bromocriptine and amantadine have been tried for the symptomatic treatment of cocaine withdrawal but have been shown to have little effect (Eiler, Schaefer, Salstrom, & Lowery, 1995; Morgan, Kosten, Gawin, & Kleber, 1988; Tennant & Sagherian, 1987).

Antidepressants aimed at treating the dysphoria associated with cocaine withdrawal have also produced equivocal results (Giannini, Loiselle, & Giannini, 1987; Tennant, Jr. & Tarver, 1984)

Vaccines

There is a cocaine vaccine being used in clinical trials and a methamphetamine vaccine in the preclinical stage (Kosten & Domingo, 2013). The mechanism of action for vaccine-induced antibodies is sequestration of drug molecules, thereby slowing or preventing contact with target sites such as transporters or receptors. The cocaine vaccine, referred to as TA-CD, consists of succinyl norcocaine linked to recombinant cholera toxin B-subunit protein; it induces antibodies that prevent cocaine from crossing the blood-brain barrier. Phase I and initial Phase II studies demonstrated safety and acceptable levels of antibody production (Kosten et al., 2002; Martell, Mitchell, Poling, Gonsai, & Kosten, 2005; Martell et al., 2009). In a human laboratory study, Haney et al. found that the TA-CD vaccine substantially decreased smoked cocaine's intoxicating effects in participants who were above the sample median in antibody generation (Haney, Gunderson, Jiang, Collins, & Foltin, 2010). The National Institute on Drug Abuse (NIDA) is supporting a multicenter, double-blind, placebo-controlled trial of the TA-CD vaccine; the results are not yet available (clinicaltrials.gov registration number NCT00969878).

The methamphetamine vaccine is still in preclinical development. It uses a tetanus toxoid carrier linked by a succinyl group to methamphetamine and combined with a new, phospholipid adjuvant which targets toll-like receptor 4 (Ishizaka & Hawkins, 2007). Preliminary results in mice indicate good levels of antibody production and attenuation of methamphetamine-induced conditioned place preference and locomotor activity (Shen et al., 2013). It is anticipated that approval for Phase I clinical trials will occur by 2015.

Conclusions

Stimulant-use disorders remain prevalent and can result in both short-term and long-term adverse consequences. The search for an effective medication continues, and until one is found, the mainstay of treatment remains behavioral interventions.

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Highlights for Psychostimulant addiction treatment

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- For psychostimulants, there is no corresponding form of agonist maintenance that has met criteria for regulatory approval or generally accepted use.
- Stimulant-use disorders remain prevalent and can result in both short-term and long-term adverse consequences.
- The mainstay of treatment remains behavioral interventions.

Table

Clinical trials in psychostimulant treatment

Authors	Study design	Sample size/ Population	Primary Objective	Findings/ Authors' Conclusions
<i>Naltrexone</i>				
Jayaram-Lindstrom et al., 2008	Double-blind placebo-controlled randomized crossover laboratory study: naltrexone (50 mg)	20 amphetamine-dependent patients	To assess the effects of naltrexone (50 mg) on subjective, physiological, and biochemical responses to dexamphetamine (30 mg).	Naltrexone significantly attenuated the subjective effects of dexamphetamine ($p<0.001$). Pretreatment with naltrexone significantly blocked the craving for dexamphetamine ($p<0.001$). There was no difference between the groups on the physiological measures.
<i>Disulfiram/ana tabuse</i>				
George et al., 2000	Double-blind placebo-controlled randomized clinical trial: disulfiram vs. placebo	20 opioid and cocaine dependent subjects (N=20) induced onto buprenorphine maintenance	To determine the efficacy of disulfiram on cocaine dependence in buprenorphine-maintained subjects.	Weeks of cocaine abstinence was significantly greater and the number of days to achieving 3 weeks of continuous cocaine abstinence was significantly lower on disulfiram versus placebo. The number of cocaine-negative urine tests during the trial were also higher on disulfiram (14.7) than on placebo (8.6); subjects in the disulfiram group had consistently higher rates of cocaine-negative urine tests in each 3-week interval and the increase over time was faster in the disulfiram compared with placebo.
Carroll et al., 2004	Double-masked (for medication) randomized clinical trial; 2 by 2 design: disulfiram and placebo with CBT and interpersonal psychotherapy (IPT)	Individuals meeting the criteria for current cocaine dependence (N=121)	To compare the effectiveness of disulfiram to placebo in reducing cocaine use and to compare the effectiveness of 2 active behavioral therapies- CBT and IPT in reducing cocaine use.	Disulfiram and CBT are effective therapies for general populations of cocaine-dependent individuals. Disulfiram seems to exert a direct effect on cocaine use rather than through reducing concurrent alcohol use.
Carroll et al., 2012	Double-blind (for medication) placebo-controlled randomized clinical trial, factorial (2x2) trial with 4 treatment conditions	Community-based methadone maintenance program participants (N=112)	To determine if disulfiram is efficacious in reducing cocaine use among individuals who use versus abstain from alcohol both with and without Twelve Step Facilitation (TSF).	TSF appears feasible in this methadone maintenance program and was associated with modest reductions in cocaine use. Support for the efficacy of disulfiram was weaker, as it appeared effective only for those without a current alcohol use

Authors	Study design	Sample size/ Population	Primary Objective	Findings/ Authors' Conclusions
				disorder.
Oliveto et al.,2011	Double-blind placebo-controlled randomized clinical trial	161 cocaine- and opioid-dependent volunteers in a 14-week trial at two sites	To examine the dose-related efficacy of disulfiram for treating cocaine dependence in methadone-stabilized cocaine dependent participants.	Disulfiram may be contraindicated for cocaine dependence at doses <250 mg/day. Whether disulfiram at higher doses is efficacious in reducing cocaine use in dually cocaine and opioid dependent individuals needs to be determined.
Kosten et al.,2013	Double-blind placebo-controlled randomized clinical trial	Cocaine- and opioid-codependent (DSM-V) subjects (N=74) stabilized on methadone for 2 weeks	To determine if a variant in the gene encoding D β H decreases disulfiram effectiveness in the treatment of cocaine dependence.	The DBH genotype of a patient could be used to identify a subset of individuals for which disulfiram treatment might be an effective pharmacotherapy for cocaine dependence.
Spellicy et al., 2013	Placebo-controlled randomized clinical trial: disulfiram (250 mg/day) vs. placebo	Cocaine and opioid codependent (DSM-IV) patients stabilized on methadone; disulfiram (N=31) or placebo (N=37)	To examine whether functional variants in the ankyrin repeat and kinase domain-containing 1 (ANKK1) and/or the dopamine receptor D2 (DRD2) genes interact with response to treatment with disulfiram.	A patient's genotype for ANKK1, DRD2, or both, may be used to identify individuals for whom disulfiram may be an effective pharmacotherapy for cocaine dependence.
Nich et al.,2004	Two pooled randomized clinical trials	Cocaine-dependent subjects (N=191; 36% female)	To evaluate differential response to disulfiram treatment of cocaine dependence by sex.	Men treated with disulfiram had better outcomes than those who were not. Women had an intermediate outcome regardless of whether they received disulfiram.
<i>Agonist-like replacement therapy</i>				
Grabowski et al., 2001	Double-blind placebo-controlled randomized clinical trial: SR dextroamphetamine sulfate, 15 to 30 mg vs. placebo	Cocaine-dependent subjects (N=128) in a 12-week trial	To determine if a dextroamphetamine sulfate agonist treatment regimen improved retention and reduced illicit drug use.	Retention was best for the 15- to 30-mg group, whereas the proportion of BE-positive urine screens was, from lowest to highest, 30 to 60 mg, 15 to 30 mg, and placebo at study end.
Galloway et al.,2011	Double-blind placebo-controlled randomized clinical trial: SR <i>d</i> amphetamine 60 mg vs. placebo	Treatment-seeking individuals with methamphetamine (MA) dependence (N=60)	To determine the safety and efficacy of SR <i>d</i> AMP in treating MA dependence.	Subjects taking d-AMP did not reduce their use of MA; significant reductions observed in withdrawal and craving scores in this group support the need for further exploration of d-AMP, possibly at higher doses.
Mooney et al.,2009	Double-blind placebo-controlled randomized clinical trial: placebo (0mg, 6x/day); IR	82 cocaine-dependent individuals in 3 groups: placebo (n=27), IR methamphetamine	Proof-of-concept study to evaluate the safety, tolerability, and effectiveness of methamphetamine as a	SR methamphetamine significantly reduced cocaine use and craving. Additional research is warranted to develop

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	methamphetamine (5mg, 6x/day); SR methamphetamine (30 mg first pill, 1x/day; 0mg 5x/day)	(n=30), SR methamphetamine (n=25)	candidate treatment for cocaine dependence.	and evaluate agonist-like medications that may effectively treat cocaine dependence.
Grabowski et al., 1997	Double-blind placebo-controlled randomized clinical trial; methamphetamine vs. placebo	Cocaine-dependent subjects - 40 enrolled, 24 completed	To investigate the efficacy of methylphenidate in the treatment of cocaine dependence.	The two groups had equivalent retention (methylphenidate 48% and placebo 42%) and similar cocaine use outcomes (40% BE-positive urine screens). There were no significant adverse effects. The doses were sufficient to permit detection of psychoactive effects ("stimulant," "more energy") and side effects ("jitteriness," "eating less") without increased "craving."
Miles et al., 2013	Parallel-group, double-blind, randomized placebo-controlled trial; methamphetamine vs. placebo	Amphetamine-/methamphetamine-dependent, aged 16-65 years. 79 randomized, 27 completed	To assess the efficacy of methylphenidate as a substitution therapy for amphetamine/methamphetamine dependence.	The trial failed to replicate earlier findings suggesting that methylphenidate was superior to placebo. The low retention rate confounded the ability to draw firm conclusions about efficacy. The higher retention rate was observed in the methylphenidate arm.
Dackis et al., 2003	Open label laboratory study	7 subjects	To test the safety of IV cocaine (30 mg) in combination with modafinil.	Co-administering modafinil and a single dose of IV cocaine is not associated with medical risk in terms of blood pressure, pulse, temperature, or electrocardiogram measures. Furthermore, pretreatment with modafinil did not intensify cocaine euphoria or cocaine-induced craving.
Dackis et al., 2012	Double-blind placebo-controlled randomized clinical trial: modafinil 0 mg/day, 200 mg/day, or 400 mg/day	Patients (N=210) actively using cocaine at baseline were randomized to 8 weeks of) combined with once-weekly CBT	To study modafinil in cocaine dependence.	No significant differences between modafinil and placebo patients in cocaine abstinence, based on urine BE levels, craving, cocaine withdrawal, retention, and tolerability except male patients treated with 400 mg/day tended to be more abstinent than their placebo-treated counterparts.
Anderson et al., 2012	Double-blind placebo-controlled randomized clinical trial: placebo vs. modafinil 200 or 400 mg	Treatment-seekers meeting DSM-IV diagnosis of methamphetamine dependence; (N=210; 68 placebo, 72	To test modafinil for efficacy in decreasing use in methamphetamine-dependent participants, compared to placebo.	Modafinil, plus group behavioral therapy, was not effective for decreasing methamphetamine use, but the study is probably inconclusive because of

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		modafinil 200mg; 70 modafinil 400mg; 12 weeks of treatment and 4-week follow-up		inadequate compliance with taking medication.
Shearer et al., 2009	Double-blind placebo-controlled randomized clinical trial: modafinil (200 mg/day) vs. placebo	Methamphetamine- dependent subjects (N=80): modafinil (n=38) or placebo (n=42); 10 weeks of treatment and 12 weeks post-treatment follow-up	To examine the safety and efficacy of modafinil compared to placebo in the treatment of methamphetamine dependence and to examine predictors of post-treatment outcome.	Modafinil demonstrated promise in reducing methamphetamine use in selected methamphetamine-dependent patients. The study findings support definitive trials of modafinil in larger multi-site trials.
Schmitz et al., 2012	Parallel-group, double-blind, randomized placebo- controlled trial: groups: placebo, modafinil 400 mg, d-amphetamine 60 mg; modafinil 200 mg plus d- amphetamine 30 mg	73 subjects with cocaine dependence in four treatment arms for 16 weeks	To determine if the combination of modafinil and d- amphetamine, at low doses, would show equivalent or greater benefit in reducing cocaine use compared to higher doses of each individual medication or placebo.	Data from this preliminary investigation failed to provide evidential support for conducting a larger study of this dual- agonist medication combination for treatment of cocaine dependence.
<i>Other medications</i>				
Oliveto et al., 2001	Single-blind, placebo-controlled laboratory study: bupropion	7 male and 3 female cocaine-abusing volunteers (age 26- 42)	To examine the interactions between cocaine and the possible treatment agent bupropion.	These results suggest that bupropion does not alter the acute subjective or cardiovascular effects of cocaine in a robust manner.
Stoops et al., 2012	Randomized, within-subject, placebo-controlled, double-blind laboratory study: bupropion	8 cocaine-using adults	To determine the influence of acute bupropion pre-treatment on subject-rated effects and choice of intranasal cocaine versus money.	The atypical antidepressant, bupropion, acutely appears to reduce preference for intranasal cocaine versus a small amount of money but to increase reported positive experiences of the drug.
Elkashaf et al., 2008	Double-blind placebo-controlled randomized clinical trial: bupropion vs. placebo	Treatment-seekers with DSM-IV diagnosis of methamphetamine dependence (N=151) in 12 weeks of treatment and a 30- day follow-up	To test bupropion for efficacy in increasing weeks of abstinence in methamphetamine- dependent patients, compared to placebo.	These data suggest that bupropion, in combination with behavioral group therapy, was effective for increasing the number of weeks of abstinence in participants with low-to-moderate methamphetamine dependence, mainly male patients, regardless of their comorbid condition.
Coffin et al., 2013	Double-blind placebo-controlled randomized clinical trial: aripiprazole vs. placebo	Actively using, methamphetamine- dependent adults (N=90) in 12 weeks treatment and 3- month follow-up	To test aripiprazole for efficacy in decreasing methamphetamine use compared to placebo.	Compared with placebo, aripiprazole did not reduce methamphetamine use significantly among actively using, dependent adults.
Sulaiman et al., 2013	Placebo-controlled randomized clinical trial: aripiprazole (5- 10 mg daily) vs. placebo	37 methamphetamine dependent patients with history of psychosis received aripiprazole (N=19)	To determine the efficacy and safety of aripiprazole for treatment of psychosis, retention and abstinence	Aripiprazole was no more effective than placebo in maintaining abstinence from

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		or placebo (N=18) for 8 weeks	in patients with methamphetamine dependence.	methamphetamine use. However, it facilitated treatment retention and reduced the severity of psychotic symptoms. Aripiprazole was found to be generally safe and well tolerated.
Cruickshank et al., 2008	Double-blind placebo-controlled randomized clinical trial: mirtazapine vs. placebo	31 participants (18 placebo, 13 mirtazapine) meeting DSM-IV criteria for amphetamine-type stimulant dependence and reported use of amphetamine or methamphetamine during the prior 72 hours; 52% completed the 2-week medication phase	To examine whether mirtazapine improves retention and alleviates methamphetamine withdrawal symptoms in an outpatient setting.	Results suggest that mirtazapine does not facilitate retention or recruitment in outpatient methamphetamine withdrawal treatment, although recruitment may have been insufficient to identify a significant treatment effect.
Newton et al., 2012	Randomized, within-subject, placebo-controlled, double-blind laboratory study: doxazosin	Non-treatment seeking, cocaine-dependent volunteers (N=13 completed)	To evaluate the effect of the noradrenergic $\alpha(1)$ receptor antagonist doxazosin on the positive subjective effects of cocaine.	Medications that block noradrenergic α_1 receptors, such as doxazosin, may be useful as treatments for cocaine dependence, and should be evaluated further.
Shorter et al., 2013	Double-blind placebo-controlled randomized clinical trial: doxazosin (8mg/day) vs. placebo	Cocaine dependent subjects (N=105 screened; N=35 assigned to receive either doxazosin or placebo for 13 weeks)	To examine the efficacy of doxazosin in reducing cocaine use in treatment-seeking cocaine dependent persons.	This pilot study suggests the potential efficacy of doxazosin when rapidly titrated in reducing cocaine use.
Eiler et al., 1995	Double-blind placebo-controlled randomized clinical trial: bromocriptine vs. placebo	Cocaine-dependent male veterans without other drug dependence (N=29)	To examine the efficacy of bromocriptine in management of cocaine abstinence symptomatology.	No apparent advantage to receiving bromocriptine versus placebo during the first 3 weeks following cocaine use cessation with the possible exception of changes in activity and appetite level.
Morgan et al., 1988	First 2 days, blinded cross-over (1 day placebo, 1 day amantadine), remaining 28 days given a prescription for amantadine 300mg	Treatment-seeking patients meeting DSM-III criteria for cocaine abuse, had used cocaine within the last 10 days, and sought treatment for cocaine abuse (N=12)	To examine the effect of amantadine on a) acute and short-term craving, b) cocaine use, and c) compliance with outpatient treatment.	At 14 days mean craving scores decreased to less than 50% of baseline ($p<0.01$). The majority of patients remained in study through the 14 th day, there was a 50% drop-out between days 14–23. Amantadine may be effective in treating the early phase of cocaine withdrawal. Well controlled clinical trials are required.
Tennant & Sagherian, 1987	Double-blind randomized trial: amantadine vs. bromocriptine	Cocaine-using subjects (N=14)	To compare amantadine hydrochloride and bromocriptine mesylate for withdrawal from cocaine dependence.	Both amantadine and bromocriptine appear effective in alleviating the symptoms of cocaine withdrawal. In doses higher than previously reported, however,

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				bromocriptine caused enough side effects to produce treatment dropouts; neither drug produced euphoria.
Giannini et al., 1986	Open field trial; desipramine vs. active placebo (diphenhydramine 25mg)	20 chronic cocaine and 20 phencyclidine abusers, who discontinued their abuse	To compare desipramine and an active placebo in separate populations of chronic cocaine and phencyclidine abusers.	Subjects who received desipramine showed a decrease in depressive symptoms after a 20–40 day period regardless of whether they abused phencyclidine or cocaine.
Tennant & Tarver, 1984	Double-blind, placebo-controlled randomized trial: desipramine vs. placebo	Cocaine-dependent subjects (N=22; 11 per group)	To determine if desipramine is effective treatment for withdrawal from cocaine dependence.	Although desipramine appears to be no more effective than placebo in withdrawal from cocaine use or suppression of withdrawal scores, it may be useful in the long-term treatment of this condition.
Vaccines				
Kosten et al., 2002	Double-blind placebo-controlled randomized phase I clinical trial	Former cocaine abusers (N=34)	To assess the safety and immunogenicity of a therapeutic cocaine vaccine TA-CD.	The therapeutic vaccine was well tolerated with dose related increases in antibody levels, and a high proportion of patients recruited into the study were retained.
Martell et al., 2005	Open label, 14-week, dose-escalation study	Cocaine dependent subjects (N=18)	To evaluate the safety, immunogenicity, and clinical efficacy of a novel human cocaine vaccine (TA-CD).	The conjugated cocaine vaccine was well tolerated and cocaine specific antibodies persisted at least six months. The likelihood of using cocaine decreased in subjects who received the more intense vaccination schedule.
Martell et al., 2009	A 24-week, phase 2b, randomized, double-blind, placebo-controlled trial with efficacy assessed during weeks 8 to 20 and follow-up to week 24	Methadone-maintained subjects (N=115)	To evaluate the immunogenicity, safety, and efficacy of a novel cocaine vaccine to treat cocaine dependence	Attaining high (≥ 43 microg/mL) IgG anticocaine antibody levels was associated with significantly reduced cocaine use, but only 38% of the vaccinated subjects attained these IgG levels and they had only 2 months of adequate cocaine blockade. Thus, we need improved vaccines and boosters.

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Haney et al., 2010	Human laboratory study	Cocaine-dependent men not seeking drug treatment (=10)	To measure the relationship between antibody titers and the effects of smoked cocaine on ratings of intoxication, craving, and cardiovascular effects.	The TA-CD vaccine substantially decreased smoked cocaine's intoxicating effects in those generating sufficient antibody. These data support further testing of cocaine immunotherapy as a treatment for cocaine dependence.

The following reviews were included in the manuscript but not in this table: Garbutt, 2010; Herin et al., 2010; Mereu et al., 2013; Sofuoglu et al., 2013; Soares et al., 2003; Lima et al., 2003; Pani et al., 2011; Sabioni et al., 2013; Minozzi et al., 2008; Lima et al., 2002; Gardner & Kosten, 2007; Kosten & Domingo, 2013; Ishizaka & Hawkins, 2007.

CBT – Cognitive Behavioral Therapy; BE – benzoylcegonine; SR – sustained release; IR – immediate release; IV – intravenous;