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Psychostimulant Treatment of Cocaine Dependence

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Synopsis

Cocaine dependence continues to be a significant public health problem and no clearly effective pharmacotherapy has yet been identified. Substitution pharmacotherapy is an effective approach for treating opioid and nicotine dependence, and accumulating evidence indicates that stimulant pharmacotherapy for cocaine dependence is a promising strategy. Broadly, stimulant medications that produce behavioral arousal, and medications across several therapeutic classes can be considered psychostimulants. To date, the available evidence is strongest for amphetamine analogs or dopaminergic agents combined with contingency management behavioral interventions as potential psychostimulant treatments for cocaine dependence. Most psychostimulants are controlled substances with inherent risks of misuse and diversion, and their use in patients with active substance use disorders is complex. As stimulant substitution treatment models for cocaine dependence are developed, particular attention to patient risk stratification is needed.

Keywords

Cocaine dependence; Psychostimulant; Substance abuse

Introduction

Cocaine dependence continues to be a substantial public health problem in the US, yet no clearly effective pharmacotherapy has been identified. There are approximately 1.6 million current users of cocaine in the US,[1] and the past-year prevalence of cocaine dependence is estimated to be 1.1%[2]. Controlled trials of behavioral treatments for cocaine dependence yield abstinence rates of up to 30%,[3] with the majority of patients continuing to use cocaine. Scores of double-blind, placebo-controlled pharmacotherapy clinical trials for cocaine dependence have been conducted, [4–6] testing agents drawn from a wide variety of medication classes. Stimulants have shown promise as a treatment for cocaine dependence despite resistance in the field to using controlled substances as therapeutic agents for addictive disorders.

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Psychoactive drugs that cause addiction generally do so by increasing dopamine release within the nucleus accumbens.[7] Cocaine binds to the dopamine transporter and inhibits catecholamine reuptake,[8] directly increasing synaptic dopamine levels in the meso-cortico-limbic system. The increased levels of dopamine in the synaptic cleft result in increased activation of type 1 and type 2 dopamine receptors. Although the behavioral effects of cocaine are attributed primarily to the blockade of dopamine reuptake, cocaine also blocks the reuptake of the other major monoamines neurotransmitters, norepinephrine and serotonin.

Stimulant medications can be defined broadly as agents that produce behavioral arousal, typically acting, either directly or indirectly, through a sympathomimetic mechanism of action, stimulating alpha- and beta-adrenergic receptors or increasing dopamine and norepinephrine in the synaptic cleft. Stimulant medications available in the US for psychiatric treatment include amphetamine analogs, methamphetamine, methylphenidate, modafinil, and armodafinil. Other sympathomimetics that are available for short-term appetite suppression include benzphetamine, phentermine, diethylpropion, phenmetrazine, phendimetrazine, and mazindol. However, there are other medications, not usually classified as stimulants, that affect catecholamine reuptake and have some stimulant-like properties. Certain antidepressant medications, such as bupropion, which blocks the reuptake of dopamine and norepinephrine, have weak stimulant properties. Drugs such as levodopa increase dopamine release into the synaptic space in a manner similar to stimulant medications, but do not cause behavioral activation and for the purposes of this review will be discussed as dopamine agonists. As a class of medications, classical psychostimulants, including the amphetamines and methylphenidate, have a rapid onset of action, immediate behavioral effects, and the propensity to induce tolerance, all of which present a risk of misuse and dependence in vulnerable individuals, and have been classified as controlled drugs and their distribution and use are regulated by state and federal agencies.

Substitution pharmacotherapy, which has been proven effective for opioid [9] and nicotine [10] dependence, is a plausible strategy for treating cocaine dependence. Conceptually, the goal of substitution pharmacotherapy is to replace a drug of abuse with rapid onset and a brief half-life with an agent that has a more gradual onset of action and long half-life, resulting in less intoxication and withdrawal, reducing the cycle of compulsive use. Successful examples of this approach include the use of methadone or buprenorphine for the treatment of opioid dependence and the use of transdermal nicotine or varenicline for nicotine dependence. Long-acting replacement medications reduce craving and potentially blunt the effects of the primary substance by either receptor blockade (buprenorphine or varenicline) or inducing high levels of physiological tolerance (methadone). Since cocaine is a short-acting psychostimulant with a rapid onset of action, a potential treatment strategy for cocaine dependence would be to substitute a longer-acting psychostimulant medication with a slower onset of action.

Neurobiology of stimulant treatment of cocaine dependence

The concept of reinforcement is central to understanding the mechanism of addiction. A reinforcer can be defined operationally as any event that increases the probability of a response. When a drug is said to have reinforcing effects, exposure to the drug makes it likely that the animal or human will work to be re-exposed to the drug. For most substances that have addictive potential, the mechanism of reinforcement is thought to be via dopamine release in the nucleus accumbens.

The acute dosing of amphetamine has been associated with priming effects for rats previously trained to self-administer cocaine. Acute administration of dextroamphetamine

into the basolateral amygdala, in combination with conditioned cue presentation, to rats trained to self-administer cocaine has been shown to potentiate reinstatement of cocaine-seeking behavior.[11] Amphetamine infusion in the absence of conditioned cues failed to reinstate the extinguished response. The facilitation of conditioned-cue reinstatement produced by amphetamine was apparent only during the initial half hour of the test session. These results suggest that while acute administration of amphetamine may potentiate cocaine reinforcement, more chronic exposure to amphetamine does not.

Animal laboratory studies have demonstrated that sustained dextroamphetamine administration can attenuate the reinforcing effects of cocaine. Dextroamphetamine has been shown to produce dose-dependent reductions in cocaine self-administration in rats.[12] In monkeys, oral dextroamphetamine pretreatment decreased responding for a sweetened cocaine fluid.[13] Dextroamphetamine administered by slow intravenous infusion has been shown to decrease cocaine self-administration in rhesus monkeys in a dose-dependent manner, possibly by attenuating the reinforcing effects of cocaine.[14, 15] Further work with monkeys has suggested that continued treatment with dextroamphetamine may be necessary to produce a sustained reduction in the reinforcing effects of cocaine.[16] These preclinical data suggest that amphetamine administration must be of a sufficient dose and duration to affect cocaine reinforcement.

Human laboratory experiments have evaluated the effects of stimulant administration on models of cocaine self-administration. Initial studies investigated the possibility that stimulant treatment of cocaine-dependent patients would worsen cocaine craving and use. In a combination clinical trial and human lab study, Grabowski et al.[17] found that methylphenidate did not “prime” patients to use cocaine. Methylphenidate has been shown to be safe and not associated with increased cocaine craving or stimulant-related euphoria in the human lab.[18] Dextroamphetamine has been shown to be safe and well tolerated when co-administered with cocaine, and attenuates some of the subjective effects of cocaine.[19] Dextroamphetamine has also been shown to alter cocaine self-administration, most likely by altering the reinforcing effects of cocaine.[20] These human laboratory experiments support to potential utility of stimulant treatment of cocaine dependence.

In current medical practice, the most common clinical use of psychostimulant medication is to treat attention-deficit/hyperactivity disorder (ADHD). In patients with ADHD, stimulants have been shown to be preferred to placebo using a laboratory choice procedure, although this preference is thought to be due to symptom relief rather than abuse potential.[21] In the human lab, methylphenidate administration has been shown to reduce cocaine self-administration in individuals with and without attention deficit/hyperactivity disorder (ADHD).[22] These results suggest that stimulant pharmacotherapy is a potential approach for treating co-occurring ADHD and cocaine dependence.

Brain imaging studies of cocaine-dependent individuals have been used to examine the potential mechanism for psychostimulant pharmacotherapy of cocaine dependence. Functional MRI imaging has shown methylphenidate to be associated with robustly decreased stop signal reaction time, an index of improved control, in cocaine-dependent patients, a population in which inhibitory control is impaired.[23] Methylphenidate has also been shown using functional MRI imaging to increase responses to a salient cognitive task, and these improvements were correlated with attenuation of anterior cingulate cortex hypoactivation.[24] Using PET and 2-fluoro-D-glucose (FDG) to measure brain glucose metabolism as a marker of brain function, methylphenidate has been shown to attenuate brain reactivity to cocaine-cues.[25] Brain imaging using the PET raclopride displacement procedure has shown that deficient dopamine transmission is associated with failure to respond to behavioral treatment. [26]. Brain imaging of cocaine-dependent individuals

receiving psychostimulants is at an early stage of development, but the initial results are quite promising in terms of both understanding the brain physiological deficits associated with cocaine dependence, as well as the potential therapeutic mechanisms of stimulant pharmacotherapy. If deficient dopamine transmission predicts poor response to behavioral interventions, then stimulant medication treatment could potentially reverse this deficit.

The association of deficient dopamine signaling with poor response to behavioral treatment[26] in particular highlights the proposed mechanism by which stimulant medications may be effective for treating cocaine dependence. Intact dopamine signaling is required for response to naturally-occurring (e.g., social or work relationships) or therapeutically manipulated (e.g., vouchers) contingencies. In a dopamine deficient state, non-cocaine rewards are not as salient as the rewarding effects of cocaine. Stimulant medication may correct the deficits in dopaminergic signaling in cocaine-dependent individuals, and thereby enhancing dopamine release in response to environmental contingencies, thereby improving the salience of competing reinforcers to cocaine.

Stimulant pharmacotherapy for cocaine dependence

Double-blind placebo-controlled trials of stimulant medications for cocaine dependence are listed in table 1. The studies, arranged by therapeutic drug class, are discussed below.

Amphetamines

Amphetamines cause release of monoamines, in particular dopamine, and also blocks monoamine reuptake.[27] These actions are similar to cocaine (dopamine reuptake blockade), although the half-life of amphetamines, in particular long-acting formulations, [28] are much longer than cocaine.

Dextroamphetamine has been evaluated in outpatient clinical trials for cocaine dependence. Grabowski et al.[29] evaluated dextroamphetamine in two escalating dosing schedules (15 to 30 mg daily and 30 to 60 mg daily) to placebo for the treatment of cocaine dependence in 128 outpatients. Retention was best for the 15 to 30 mg group and the proportion of positive urine toxicology samples was lowest for the 30 to 60 mg group, followed by the 15 to 30 mg group, and then the placebo group. Grabowski et al.[30] also compared dextroamphetamine in two different escalating dose regimens to placebo for the treatment of cocaine- and opioid-dependent patients (n=120) receiving methadone maintenance treatment. The higher dose group of dextroamphetamine (30 to 60 mg per day) was superior to both the lower dose group (15 to 30 mg per day) and placebo. Shearer et al.[31] evaluated dextroamphetamine for the treatment of cocaine dependence in a sample of 30 patients. No between group differences were detected, although the small sample size suggests lack of statistical power to do so. Participants in the active medication group experienced reductions in the proportion of cocaine positive urines, craving scores, and other measures of cocaine dependence severity, while those in the placebo group did not improve on these measures.

Methamphetamine, an amphetamine analogue, with a similar mechanism of action to cocaine, has been studied for the treatment of cocaine dependence. Mooney et al. [32] reported that in 82 cocaine-dependent outpatients the sustained release preparation of methamphetamine was found to be associated with lower rates of cocaine-positive urine samples and greater reduction in craving than placebo, while the immediate-release formulation of methamphetamine was not superior to placebo for cocaine use outcomes. Despite these promising results, no other randomized placebo-controlled clinical trials have tested the use of methamphetamine for cocaine dependence.

Mazindol, a sympathomimetic amine similar to amphetamine, is a catecholamine reuptake blocker, and was among the first stimulant medications studied for the treatment of cocaine dependence. Margolin et al.[33] conducted a small double-blind placebo-controlled trial of mazindol in 37 opioid-dependent methadone maintenance patients with cocaine abuse and found no statistically significant difference between treatment groups. In a double-blind placebo-controlled trial, Stine et al.[34] also evaluated mazindol in 43 cocaine-dependent outpatients and found no difference between treatment groups. These trials for testing mazindol did not yield significant results. However, given the relatively small sample sizes, these results are not likely to be definitive.

The results for dextroamphetamine and methamphetamine as potential treatments for cocaine dependence are promising, but there have been no large-scale, multi-site trials confirming the results. A possible explanation for the lack of confirmatory studies despite promising initial results is that the field is resistant to investigating a controlled substance as a treatment for cocaine dependence. Other agents, with less or no abuse potential, including modafinil (discussed below)[35, 36] and vigabatrin,[37] proceeded relatively quickly to multi-site trials based on the results of positive findings in single-site studies.

Dopamine Agonists

Medications that directly stimulate dopamine receptors or increase the levels of synaptic dopamine have a mechanism of action similar to stimulants, although they do not necessarily have the same activating effects on behavior. Mooney et al. [38] reported on two trials testing the combination of levodopa and carbidopa in 189 cocaine-dependent outpatients. Levodopa-carbidopa was well tolerated by cocaine-dependent patients, but did not improve cocaine use outcomes compared to placebo. These results contrast the use of levodopa when combined with contingency management (discussed below).

Methylphenidate

Methylphenidate is structurally related to the amphetamines, but differs in mechanism of action. The stimulant properties of methylphenidate are presumed to be mainly due to inhibition of dopamine reuptake by binding to the dopamine transporter, while the primary action of amphetamine is to cause dopamine release into the synaptic cleft, and secondarily block catecholamine reuptake.[39] Reuptake inhibition of norepinephrine by blockade for the norepinephrine transporter is presumed to be an important secondary mechanism of action of methylphenidate. The main clinical use of methylphenidate is, like for amphetamine, for the treatment of ADHD.

Methylphenidate has been investigated as a treatment for cocaine dependence. In a human lab study, methylphenidate has been shown to be safe and well tolerated in doses up to 90 mg daily when co-administered with cocaine.[40] Grabowski et al.[17] compared methylphenidate to placebo for the treatment of cocaine dependence in 24 outpatients. Retention was equivalent between groups, with no significant differences in cocaine use outcomes, although statistical power was limited due to the small sample size. No significant adverse effects were reported. Larger, adequately powered studies examining the effect of methylphenidate on cocaine dependence have not been conducted.

Methylphenidate has also been studied as a treatment for cocaine dependence co-occurring with ADHD. Schubiner et al.[41] studied methylphenidate in comparison to placebo for the treatment of 48 cocaine-dependent attention-deficit/hyperactivity adults (ADHD) and found significantly greater ADHD symptom relief in the methylphenidate group, but no group differences in cocaine use outcomes. Levin et al.[42] evaluated methylphenidate in comparison to placebo for the treatment of co-occurring ADHD and cocaine dependence in

106 outpatients. There were no significant between group differences in ADHD symptom response or retention. While the primary cocaine use outcome measure was negative, a secondary analysis using logistic regression found that methylphenidate was associated with a lower probability of cocaine positive urine samples. Secondary analyses demonstrated that in the methylphenidate group, ADHD treatment responders, were more likely to have a reduction in cocaine use as compared to non-ADHD responders. These results suggest that methylphenidate has therapeutic effects on ADHD symptoms even in active cocaine users, and that ADHD symptom response may be important for improving cocaine use outcomes in patients with co-occurring ADHD and cocaine dependence.

Modafinil and Armodafinil

Modafinil is a psychostimulant medication unrelated to the structure of amphetamine, and has a differing profile of pharmacologic and behavioral effects.[43] Modafinil binds moderately to dopamine and norepinephrine transporters, increasing synaptic catecholamine levels. Elevations in other neurotransmitters appear to be secondary to changes in elevations in catecholamines.

Modafinil has been studied for the treatment of cocaine dependence and has been found to be safe and well tolerated when co-administered with cocaine.[44] Dackis et al.[35] conducted a pilot study of 62 cocaine-dependent participants and found that modafinil was superior to placebo in achieving abstinence and was associated with significantly more cocaine-negative urine samples. However, the follow-up multi-site trial of 210 participants randomized to placebo, modafinil 200 mg/daily, or modafinil 400 mg daily, showed no advantage of modafinil on the primary outcome measure.[36] Secondary outcomes, including reduction of craving and the maximum number of consecutive non-use days for cocaine, favored modafinil treatment, and a *post hoc* analysis showed a significant effect of modafinil on the weekly percentage of non-use days in the subgroup of cocaine-dependent patients who did not have a history of alcohol dependence. Based on these data, modafinil does not appear to be effective for treating cocaine-dependent patients with a history of alcohol dependence, but may be effective for cocaine-dependent patients without alcohol dependence. Future studies should exclude participants with alcohol dependence.

Stimulant Antidepressants

Bupropion is a novel antidepressant medication with a chemical structure dissimilar to existing antidepressant medications, but slightly similar to the endogenous monoamine neurotransmitters dopamine and norepinephrine. The presumed mechanism of action of bupropion has evolved over time, and is now thought to be due to reuptake inhibition of dopamine and norepinephrine by blocking the respective transporters.[45] The clinical profile of bupropion is that of mild stimulating effects.

Bupropion has been studied for the treatment of cocaine dependence. Margolin et al.[46] studied the bupropion for cocaine dependence in a multisite trial with 149 participants. No differences were observed between placebo and bupropion in cocaine use, depression, or psychosocial function. However, a secondary analysis showed that among the subset of participants (n=36) with baseline depression there was a significant decrease in the proportion of urine toxicology samples positive for cocaine in the bupropion group. Shoptaw et al.[47] compared bupropion to placebo in a double-blind trial of 70 cocaine-dependent outpatients and found no differences between treatment groups. Secondary analyses found no significant differences by treatment group when controlling for baseline depression scores. The results of these two large clinical trials suggest that bupropion is not an effective treatment for cocaine dependence.

Selegiline is an irreversible selective inhibitor of monoamine oxidase type B (MAO-B). The inhibition of MAO-B increases the concentration of dopamine and other neurotransmitters, and is partially metabolized to *L*-methamphetamine and *L*-amphetamine. However, selegiline does not have consistent behavioral activation properties and should not be classified as a stimulant. Elkashef et al.[48] studied the use of a transdermal patch delivery system of selegiline for the treatment of 300 cocaine-dependent outpatients in a multi-site double-blind placebo-controlled trial. No differences between selegiline and placebo were detected, suggesting that selegiline is not likely to have a role for treating cocaine dependence.

Dopaminergic augmentation of contingency management

Dopaminergic medications have been tested in combination with contingency management behavioral interventions (see table 2). The theoretical framework for this approach is that cocaine dependent individuals have difficulty responding to non-cocaine rewards, and that dopaminergic medications may normalize dopamine signaling and thereby increase the saliency of rewards offered as part of a behavioral treatment. In a clinical trial comparing levodopa-carbidopa to placebo combined with clinical management, cognitive behavioral therapy or voucher-based reinforcement therapy, levodopa combined with vouchers was associated with higher rates of abstinence and higher proportions of cocaine-free urines.[49] Levodopa-carbidopa was also evaluated in combination with three different contingency management (CM) targets (urine, medication, or attendance) and the combination of levodopa with CM-urine was associated with superior cocaine use outcomes, an effect moderated by medication compliance.[50] In a population of cocaine- and opioid-dependent methadone maintenance patients, bupropion was compared to placebo in combination with either CM or a voucher control condition, and the combination of CM with bupropion was associated with improved cocaine use outcomes as compared to bupropion alone.[51]

However, studies of antidepressant medications that block reuptake of monoamines other than dopamine have also yielded positive results as augmenters of contingency management for cocaine dependence, including citalopram[52] and desipramine.[53] These results suggest that blocking the reuptake of monoamines in general may be responsible for the mechanism of augmentation of contingency management, and not limited to dopaminergic effects per se. Further research is needed to elucidate the mechanism of the observed monoamine augmentation of contingency management treatment of cocaine dependence.

The strategy of augmenting contingency management interventions with drugs that enhance dopaminergic transmission is consistent with the hypothesis that cocaine-dependent individuals have deficient dopaminergic tone and that competing rewards to cocaine are less salient. A logical step in the development of this research would be to study more potent dopaminergic medications, such as amphetamines and methylphenidate, as augmenters of behavioral treatment.

Co-occurring ADHD and Cocaine Dependence

ADHD and cocaine dependence commonly occur. In clinical populations, the prevalence of ADHD in substance use disorder treatment settings ranges up to 24%.[54, 55] In the general population, the prevalence of adult ADHD is 4.4%, while in individuals with a substance use disorder, ADHD co-occurs at a rate of 10.8%.[56] These data indicate that co-occurring ADHD and cocaine dependence will be routinely encountered in clinical settings.

Amphetamines[57] and methylphenidate[58] are effective treatments for treating adult ADHD. Since ADHD treatment is the main current clinical use of psychostimulant medications, concerns have been raised about the potential interaction between cocaine and psychostimulants. Stimulant therapy of ADHD in childhood is associated with a reduction in

the risk for subsequent drug and alcohol use disorders.[59] However, psychostimulants increase extracellular dopamine in the brain, which is associated with both therapeutic and reinforcing effects. Volkow and Swanson,[60] identified four variables that affected the therapeutic and reinforcing effects of methylphenidate, which included:

1. dose
2. pharmacokinetics
3. individual differences in sensitivity to methylphenidate
4. context

Large doses that penetrate the blood brain barrier rapidly are associated with greater reinforcing effects, leading to the recommendation that the lowest possible dose that relieves symptoms be used, and that sustained-release preparations are preferred for individuals with a predisposition to addiction.

Addictive Potential of Psychostimulants

Stimulant medications have the potential for misuse, diversion, and addiction.[61–63] Methylphenidate and dextroamphetamine have been shown to have reinforcing effects in individuals without histories of substance use disorders[64] and individuals with stimulant abuse histories.[65] The rate of onset of a drug's effect is an important determinant of its abuse potential. In a controlled laboratory evaluation, Kollins et al.,[66] found that the sustained-release formulation of methylphenidate was associated with less ratings of “good effects” as compared to the immediate-release formulation. These findings suggest that the abuse potential of the immediate release preparation may be greater than the sustained release preparation.

Precautions in Prescribing Stimulant Medications

Misuse, diversion, and addiction are inherent risks of prescribing controlled substances, and a substantial minority of patients prescribed stimulants will divert their medications to others or misuse their own prescription.[61] An assessment of risk in a specific patient has to be determined at a specific point in time. All patients prescribed controlled substances should be assessed at each visit for signs of misuse, abuse, or addiction. Evaluations should be conducted using matter-of-fact and non-threatening questioning.

Red Flags for Diversion or Misuse

- Symptoms of intoxication or withdrawal
- Demands for a particular, usually fast acting, medication (amphetamine IR)
- “Extended-release doesn't work for me”
- Repeated lost prescriptions
- Discordant pill count
- Excessive preoccupation with securing medication supply
- Multiple prescribers
- New development of cardiac symptoms
- New onset psychosis

There are a number of strategies that can be employed to minimize the risks presented when prescribing controlled substances psychostimulant treatment to patients with cocaine dependence. All patients with substance use disorders who are prescribed controlled substances should be advised of the risk of combining prescription medication with other substances. Patients should be warned about diversion and abuse liability of prescription stimulant medications. Delayed release preparations are in general preferred over immediate release preparations for behavioral safety. Prescription of small quantities of medication at a time, with pill count reconciled at each visit. Urine toxicology and breath alcohol testing can be useful in assessing patients overall clinical status. State prescribing databases can be consulted to check for multiple prescribers. Frequent patient visits may help detect problems or a change in clinical status sooner. In general, it should be emphasized to patients to take medications regularly, not on an as needed basis, creating a structure of consistency and predictability around stimulant medication taking. Discussions with patients regarding safe storage and not advertising/sharing medications with others should occur regularly.

Conclusions

The use of stimulant medications for the treatment of cocaine dependence is an evolving scientific literature. To date, the most promising results are with the higher potency medications, the amphetamine analogues, or a combination of a dopaminergic medication with a contingency management behavioral intervention. The development of effective pharmacotherapies for opioid and nicotine dependence using an agonist replacement approach suggests that these promising findings need to continue to be vigorously investigated.

In clinical trial reports there are very few instances of cardiovascular adverse events, which suggest that for well-selected patients with cocaine dependence, stimulant replacement therapy can be safe. However, clinical trial eligibility criteria excludes most high-risk patients from participating, and introducing stimulant substitution to the wider treatment community would likely expose more vulnerable patients to the medical risks associated with stimulant treatment while using cocaine. As treatment development research moves forward, attention must be paid to helping clinicians select patients who are most likely to benefit from stimulant substitution treatment, and how to identify those at risk.

An additional concern with the use of stimulant medication treatment of cocaine dependence is prescribing controlled substances for patients with active substance use disorders. Again, within a clinical trial, medication supplies are carefully monitored and distributed in small quantities. In a community setting, misuse or diversion will be risks associated with prescribing controlled substances to patients with addictive disorders, but therapeutic strategies for monitoring and limiting that risk can be implemented.

In summary, psychostimulant pharmacotherapy is a promising line of research for the treatment of cocaine dependence, a condition for which no effective pharmacotherapy has been identified. Further research is required to confirm positive results from single-site trials, in particular the study of amphetamines as a treatment for cocaine dependence. As this literature evolves, strategies to manage the risk of prescribing controlled substances to patients with addictive disorders need to be tested and refined. Biases against using controlled substances as a treatment for cocaine dependence should be challenged, much in the way the use of agonist treatment transformed the treatment of opioid dependence despite initial resistance from the field.

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Key Points

A reinforcer, in terms of mechanisms of addiction, can be defined operationally as any event that increases the probability of a response; psychostimulants increase extracellular dopamine in the brain, which is associated with both therapeutic and reinforcing effects

In current medical practice, the most common clinical use of psychostimulant medication is to treat attention-deficit/hyperactivity disorder (ADHD). ADHD co-occurs in individuals with a substance use disorder at a rate of 10.8%

Misuse, diversion, and addiction are inherent risks of prescribing controlled substances; all patients prescribed controlled substances should be assessed at each visit for signs of misuse, abuse, or addiction.

Table 1
Psychostimulant and Dopaminergic Treatment of Cocaine Dependence: Double-Blind Placebo-Controlled Clinical Trials

First Author	Publication Year	Population	Medication	N	Results
Anderson	2009	Cocaine dependence	modafinil	210	No significant effect on primary outcome of cocaine abstinence
Dackis	2005	Cocaine dependence	modafinil	62	Modafinil associated with more cocaine-negative urines and cocaine abstinence
Elkashaf	2006	Cocaine dependence	selegiline	300	No differences between selegiline and placebo
Grabowski	1997	Cocaine dependence	methylphenidate	24	No differences between groups, limited statistical power
Grabowski	2001	Cocaine dependence	Dextroamphetamine	128	Dextroamphetamine 30–60 mg superior to 15–30 mg and placebo for negative urine drug samples
Grabowski	2004	Cocaine and opioid dependence receiving methadone	Dextroamphetamine	120	Reduction in cocaine use significant for 30–60 mg dosing of dextroamphetamine
Levin	2007	Cocaine dependence and ADHD	methylphenidate	106	Primary outcome not significant; secondary analysis showed lower probability of cocaine positive urine samples for methylphenidate group. In methylphenidate group, ADHD responders more likely to have reduction in cocaine use
Margolin	1995a	Cocaine dependence	bupropion	149	No differences between placebo and bupropion in primary analysis; depressed subgroup receiving bupropion with lower proportion positive urine toxicologies
Margolin	1995b	Cocaine abuse and opioid dependence receiving methadone	mazindol	37	No differences between placebo and mazindol, limited statistical power
Mooney	2007	Cocaine dependence	Levodopa-carbidopa	189	No difference from placebo
Mooney	2009	Cocaine dependence	methamphetamine	82	Sustained-release formulation of methamphetamine associated with less cocaine-positive urines and less craving
Schubiner	2002	Cocaine dependence and ADHD	methylphenidate	4	ADHD symptoms improved on methylphenidate, no differences on cocaine use outcomes
Shearer	2003	Cocaine dependence	dextroamphetamine	30	No between group differences, limited statistical power
Shoptaw	2008	Cocaine abuse or dependence	bupropion	70	No differences between placebo and bupropion, no impact of depressive symptoms on outcome
Stine	1995	Cocaine dependence	mazindol	43	No difference between mazindol and placebo, possible limited statistical power

Table 2

Dopaminergic Augmentation of Contingency Management Treatment of Cocaine Dependence: Double-Blind Placebo-Controlled Trials

Author	Publication Year	Population	Medication	Behavioral intervention	N	results
Poling	2006	Cocaine and opioid dependence receiving methadone	bupropion	Contingency management	106	Bupropion with contingency management more effective than bupropion alone
Schmitz	2008	Cocaine dependence	Levodopa-carbidopa	Voucher incentives, CBT, and clinical management	161	Levodopa with vouchers associated with abstinence and negative urine tests
Schmitz	2010	Cocaine	Levodopa-carbidopa	Contingency management of urine, attendance, or medication taking	136	Levodopa with CM-urine produced superior cocaine use outcomes, with effect moderated by medication compliance