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Agonist replacement therapy for cocaine dependence: a translational review

Craig R Rush[*,1,2,3] and **William W Stoops**[1,3]

[1]Department of Behavioral Science, University of Kentucky, College of Medicine, Medical Behavioral Science Building, Lexington, KY 40536-0086, USA

[2]Department of Psychiatry, University of Kentucky College of Medicine, 3470 Blazer Parkway, Lexington, KY 40509, USA

[3]Department of Psychology, University of Kentucky College of Arts and Sciences, Kastle Hall, Lexington, KY 40506, USA

Abstract

Cocaine use disorders are prevalent throughout the world. Agonist replacement therapy is among the most effective strategies for managing substance use disorders including nicotine and opioid dependence. This paper reviews the translational literature, including preclinical experiments, human laboratory studies and clinical trials, to determine whether agonist-replacement therapy is a viable strategy for managing cocaine dependence. Discussion is limited to transporter blockers (i.e., methylphenidate) and releasers (i.e., amphetamine analogs) that are available for use in humans in the hope of impacting clinical research and practice more quickly. The translational review suggests that agonist-replacement therapy, especially monoamine releasers, may be effective for managing cocaine dependence. Future directions for medications development are also discussed because the viability of agonist-replacement therapy for cocaine dependence may hinge on identifying novel compounds or formulations that have less abuse and diversion potential.

Cocaine dependence is an unrelenting public health concern worldwide. Data from the USA indicate that approximately 2 million Americans over the age of 12 years report current cocaine use [1]. In 2007, primary cocaine abuse accounted for 13% of treatment admissions in the USA according to the Treatment Episode Data Set [2]. In the EU, approximately 1.5 million people report current cocaine use [3]. While treatment admissions for cocaine represent 17% of all drug treatment admissions in the EU, rates vary by country and are as high as 45% (i.e., Spain) [3]. Despite prevention and intervention efforts, prevalence of cocaine use remains stable [1].

Cocaine use produces a number of direct health problems (e.g., psychosis and cardiovascular toxicity) [4,5], which can result in poor health outcomes. Cocaine use is also associated with a number of other health issues including smoking cigarettes, having comorbid psychological disorders and increased probability of acquiring sexually transmitted

[*]Author for correspondence: Tel.: +1 (859) 323 6130, Fax: +1 (859) 257 7684, crush2@email.uky.edu.

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infections [6–8]. Research that identifies promising therapies for cocaine dependence will have significant public health implications.

Behavioral therapies, such as contingency management and cognitive-behavioral therapy, are effective for reducing cocaine use [9–11]. However, many patients enrolled in behavioral therapies are unable to achieve significant periods of abstinence suggesting other strategies, such as pharmacotherapy, are needed [12]. An effective medication has not yet been identified for cocaine dependence even though it has been a priority for the National Institute on Drug Abuse for nearly three decades [13,14].

Considerable efforts have focused on identifying a 'cocaine antagonist' [13,15,16]. The premise of this approach is that treating patients with an antagonist will block the desired effects of cocaine (e.g., euphoria), thereby leading to the extinction of drug-taking and drug-seeking behavior [15]. Antagonist therapies such as mecamylamine and naltrexone are somewhat effective for nicotine and opioid dependence, respectively [17–19]. Several compounds attenuated the behavioral effects of cocaine in preclinical and human laboratory studies, but none has proven effective clinically [13,16,20–22]. In fact, treating cocaine-dependent individuals with some putative 'cocaine antagonists' (e.g., olanzapine and risperidone) may actually increase drug use and decrease treatment retention [20,23,24].

An alternative approach is **agonist-replacement therapy**. As the name implies, a pharmacologically similar agent is substituted for cocaine [15,20,25,26]. Treating patients with an agonist presumably suppresses withdrawal and produces tolerance to the desired effects of cocaine (e.g., euphoria) [15]. Agonist replacements also likely function as positive reinforcers for drug users, which indicate that they can be used as reinforcing stimuli in contingency management strategies to decrease illicit drug use and promote more adaptive behavior. Agonist replacement therapies are effective for nicotine and opioid dependence [27–30].

The purpose of this paper is to review the translational literature to determine the viability of agonist-replacement therapy for managing cocaine dependence. The results of preclinical experiments, human laboratory studies, and clinical trials are reviewed. The literature reviewed supports the utility of potent agonist replacement such as D-amphetamine and methamphetamine for managing cocaine use disorders. However, amphetamine analogs have significant abuse and diversion potential [31,32]. Clinicians may be reluctant to use these compounds to manage cocaine dependence because of these problems. The viability of the agonist-replacement approach for cocaine dependence may hinge on identifying novel agonist medications or formulations that have less abuse and diversion potential. Development of such formulations is where medicinal chemistry has the greatest potential to significantly impact the treatment of cocaine dependence. In order to guide medicinal chemistry research, this paper reviews the extant translational literature that determined the efficacy of novel agonist compounds or formulations of agonist-replacement therapies and provides suggestions for drug-development targets.

It is important to note that long-term drug exposure can result in physicial dependence, particularly for alcohol, opioids, benzodiazepines and barbiturates. Abrupt cessation of the drug then results in a recognizable withdrawal syndrome. With opioids, for example, long-term exposure followed by abstinence results in a withdrawal syndrome characterized by yawning, diaphoresis lacrimation, rhinorrhea, insomnia, mydriasis, piloerection, tachycardia, hypertension, nausea/vomiting, diarrhea and muscle aches/pains. Behaviorally, opioid withdrawal increases the reinforcing efficacy of opioids under a variety of behavioral procedures [33,34]. Agonist replacement therapies alleviate these symptoms and have been

shown to attenuate withdrawal-induced increases in the reinforcing effects of abused opioids, such as heroin [33].

The role of withdrawal in the maintenance of cocaine-taking behavior is much less clear. Most notably, experimenter-induced abstinence did not enhance the reinforcing of cocaine in rhesus monkeys [35,36]. Because of the uncertainty regarding the contribution of withdrawal to continued cocaine-taking behavior, the ability of agonist-replacement therapies to alleviate withdrawal is not reviewed.

Agonist-replacement therapies for cocaine dependence

An ideal agonist-replacement therapy for cocaine dependence should share some pharmacological and behavioral effects with cocaine, but have less abuse potential. Abused stimulants produce their behavioral and physiological effects via interaction with monoamine transporters (dopamine, serotonin and norephinephrine) [37–39]. Based on *in vitro* studies, stimulants can be broadly categorized into two groups by their mechanism of action at these transporters. Cocaine binds to monoamine transporters and prevents monoamine reuptake back into the pre-synaptic terminal, but it is not transported [40]. Amphetamines, by contrast, act as substrates for monoamine transporters and are transported into the nerve terminal where they promote the release of monoamines into the synapse by preventing the accumulation of neurotransmitter in storage vesicles and also by carrier-mediated exchange [41]. Amphetamines also usually function as transporter blockers, although they are less potent at inhibiting reuptake compared with their ability to act as transporter substrates [41]. Thus, cocaine and amphetamines increase extracellular monoamine levels, albeit by different mechanisms.

In this section, we review the extant literature that determined the efficacy of monoamine transporter blockers and releasers for managing cocaine dependence. Special emphasis is given to dopamine uptake blockers and releasers because this monoamine plays a prominent role in mediating the abuse-related effects of cocaine [38,42–44]. This review is limited to those transporter blockers (i.e., methylphenidate and cocaine) and releasers (i.e., D-amphetamine or methamphetamine) that are available for use in humans. By demonstrating the efficacy of these compounds, we hope to impact clinical research and practice more quickly. Limiting the present review to compounds available for use with humans is not intended to minimize the future contribution of medicinal chemistry to developing effective and acceptable agonist-replacement therapies. Accordingly, the present review concludes with a brief summary of promising agonist-replacement therapies that are currently under development.

Monoamine transport blockers

Methylphenidate, a piperidine derivative that blocks monoamine reuptake, is prescribed commonly for behavioral problems associated with attention deficit hyperactivity disorder (ADHD) and sleep disorders (e.g., excessive daytime sleepiness or narcolepsy) [45,46]. Methylphenidate and cocaine are very similar in terms of their actions at the dopamine transporter [40,47–49]. In baboons, for example, methylphenidate and cocaine produce comparable increases in synaptic dopamine levels [48]. As another example, the *in vivo* potency of methylphenidate at the dopamine transporter is comparable to that of cocaine in human brain [49]. Moreover, in humans, the regional distribution of [^{11}C] methylphenidate is almost identical to that of [^{11}C] cocaine [50]. Consistent with these neuropharmacological similarities, data from preclinical and human behavioral pharmacology studies suggest that methylphenidate and cocaine produce similar behavioral effects. Methylphenidate and cocaine function as reinforcers in laboratory animals and humans under a variety of behavioral arrangements [51–53]. The discriminative stimulus and **subjective drug effects**

of methylphenidate are virtually indistinguishable from those produced by cocaine [54,55]. Because there appears to be little, if any, difference between methylphenidate and cocaine in terms of their behavioral effects, preclinical experiments, human laboratory studies and clinical trials have been conducted to determine if methylphenidate might function as an agonist-replacement therapy for cocaine dependence.

In this section, we review the available translational studies that tested the efficacy of dopamine transport blockers, methylphenidate and cocaine, as agonist-replacement therapies for cocaine dependence. The premise for testing the effects of cocaine pretreatment is that a significant attenuation of the reinforcing effects would most likely be observed with a medication that is most similar to cocaine (i.e., the drug itself). The review of the preclinical literature is limited to those experiments that assessed the effects of agonist-replacement therapies on cocaine self-administration. The reinforcing effects of cocaine may be the single most important behavioral determinant of its abuse. By inference, then, the ability to attenuate the reinforcing effects may be a necessary characteristic of an effective pharmacotherapy for cocaine dependence [56].

The review of human laboratory studies includes those experiments that used **drug self-administration** procedures and subjective-effects questionnaires. Human laboratory experiments designed to determine the efficacy of a putative pharmacotherapy typically administer a range of doses of cocaine while participants are maintained on varying doses, including placebo, of the candidate medication [57]. Following the administration of cocaine, participants periodically complete a battery of subjective-effects questionnaires. Some of the questionnaires are standardized (e.g., Addiction Research Center Inventory), while others are investigator developed (e.g., Drug-Effect Questionnaire). The premise of these studies is that the positive subjective effects (e.g., Drug Liking) of cocaine contribute significantly to its abuse. Positive subjective effects are thought to be a proxy of the reinforcing effects of cocaine. Medications that attenuate the subjective effects of cocaine would be predicted to be effective clinically because drug taking would extinguish when the patient no longer experiences the desired effects.

Preclinical drug self-administration experiments—To our knowledge there have been four preclinical laboratory experiments that examined the reinforcing effects of cocaine in animals pretreated with cocaine or methylphenidate [58–61]. In the earliest experiment, the reinforcing effects of intravenous (iv.) cocaine (0, 0.001, 0.0032, 0.01 and 0.032 mg/kg/injection) were assessed in rhesus monkeys (n = 3) pretreated with iv. cocaine (0.32, 1.0 and 3.2 mg/kg) [61]. The reinforcing effects of cocaine were assessed in ascending and descending order in this experiment. Rates of responding for cocaine increased as an orderly, graded function of dose in both the ascending and descending dose conditions. Cocaine pretreatment dose dependently decreased rates of responding for the high cocaine dose only in the descending condition. In the second experiment, the effects of cocaine on responding maintained by limited access to food and varying doses of cocaine (0.01 or 0.056 mg/kg/injection) were assessed in rhesus monkeys (n = 9) [58]. Responding for cocaine and food decreased as a result of continuous infusions of cocaine (0.05–0.27 mg/min) plus a preload with cocaine (0.133 or 0.4 mg/kg) during the experimental session. In the third experiment, the reinforcing effects of cocaine (0, 0.032, 0.1, 0.32 and 1.0 mg/kg/injection) were assessed in rodents using a fixed-ratio five schedule of reinforcement [59]. Animals were pretreated with varying doses of methylphenidate (0, 3.2, 10 and 32 mg/kg) 60 min prior to being able to self-administer cocaine. The effects of cocaine alone were an orderly function of dose. The two higher doses of methylphenidate (10 and 32 mg/kg) decreased cocaine intake but not responding for cocaine. In the final experiment, noncontingent cocaine administration (0.32 mg/kg/h) did not affect choice of varying doses of cocaine (0–0.1 mg/kg/inject) [60].

Human drug self-administration—We know of only one study that assessed the effects of a dopamine transport blocker on the reinforcing effects of cocaine in humans [62]. In that study, cocaine-dependent patients with co-morbid ADHD (n = 7) were maintained on methylphenidate (0, 40 and 60 mg/day) [62]. The reinforcing effects of iv. cocaine (0, 16 and 48 mg) were assessed using a choice procedure wherein participants sampled a dose of cocaine (16 or 48 mg, iv.) and were then given five opportunities to choose between it and a US$2 token. Participants chose the 48-mg iv. cocaine dose four of five times during placebo maintenance. Methylphenidate maintenance (i.e., 60 mg/day) significantly reduced choice of the 48-mg iv. cocaine dose (i.e., to two of five choices).

Human subjective-effects studies—Three human laboratory studies assessed the subjective effects of cocaine in participants maintained on a dopamine transport blocker [62–64]. In the seminal study, the subjective effects of iv. cocaine (0, 25 and 50 mg) were assessed in participants maintained on oral (p.o.) cocaine (0, 25, 50 and 100 mg, four-times daily) [63]. p.o. cocaine was chosen for study in this 'proof-of-concept' experiment on the premise that a significant attenuation of the abuse-related effects would most likely be observed with a medication that is most similar to cocaine, comparable to the rationale for preclinical research testing cocaine for cocaine use disorders. The effects of cocaine are qualitatively and quantitatively similar when administered p.o. or intranasally [65,66]. In the other two studies, participants were maintained on 0, 40 and 60 mg/day or 0, 60 and 90 mg/day methylphenidate [62,64]. During each maintenance phase, a dose–response function was determined for iv. cocaine (0–50 mg). Cocaine produced prototypical stimulant-like subject-rated effects (e.g., increased ratings of Good Effects, Like Drug) that were a function of dose in each of these studies. Maintenance on p.o. cocaine or methylphenidate significantly, but only partially, attenuated cocaine-induced increases in Good Effects in each of these studies. These effects were generally limited to the lower cocaine doses. Maintenance on p.o. cocaine also significantly attenuated increases in subjective ratings of Drug Liking induced by iv. cocaine in one study [63].

Another human laboratory assessed the subjective effects of a range of doses of iv. cocaine (5–40 mg/70 kg) alone and following acute pretreatment with p.o. cocaine (0 and 300 mg/70 kg) [67]. iv. cocaine produced prototypical subjective effects (e.g., increased ratings of Good Effects). p.o. cocaine pretreatment enhanced the effects of iv. cocaine.

Clinical trials—The results of the initial clinical trials that tested methylphenidate as a putative agonist-replacement therapy for cocaine dependence are mixed. In the initial trial, cocaine-dependent patients (n = 24) were enrolled in an 11-week double-blind, placebo-controlled study of methylphenidate [68]. Patients were randomly assigned to placebo or methylphenidate (5 mg immediate release plus 20 mg sustained release). The primary outcome measure was cocaine use, verified twice weekly with drug urine tests for the cocaine metabolite, benzoylecgonine. The two groups did not differ significantly in terms of benzoylecgonine-positive urine screens (i.e., ~40%) or study retention.

Two trials tested methylphenidate as a putative agonist-replacement therapy in cocaine-dependent patients with co-morbid ADHD [69,70]. In the earlier trial, patients (n = 48) were randomly assigned to placebo or methylphenidate in a 12-week, double-blind trial [70]. The methylphenidate dose was titrated upward to a target dose of 90 mg/day. The placebo- and methylphenidate-treated groups did not differ in terms of cocaine use as verified by drug urine testing or cocaine craving. In the later trial, patients (n = 48) were randomly assigned to placebo or methylphenidate in a 14-week, double-blind trial [69]. The methylphenidate dose was titrated upward to a target dose of 60 mg/day. Methylphenidate-treated patients demonstrated a significant decrease in the probability of a cocaine-positive urine sample during the trial relative to their placebo-treated counterparts. The reason for these discrepant

findings is unknown, but the negative results could be due to the relatively small sample size of these studies.

Summary—The pharmacological and behavioral effects of methylphenidate and cocaine overlap extensively, suggesting dopamine transport blockers might function as an agonist-replacement therapy for cocaine dependence. The results of preclinical cocaine self-administration experiments are mixed regarding whether methylphenidate or cocaine pretreatment reduces drug taking. The results of human laboratory studies suggest that methylphenidate maintenance attenuates the reinforcing and subjective effects of cocaine. However, the results of clinical trials that tested the efficacy of methylphenidate as a putative agonist-replacement therapy have been disappointing. The discordance between the clinical trials and the preclinical findings may be due to more heterogeneous samples being tested in the clinical trials.

The discordance between the clinical trials and the human laboratory experiments may be due to the fact that only nontreatment seeking participants were enrolled in the human laboratory experiments. Ethicists generally recommend that only nontreatment seeking participants be enrolled in human laboratory studies that involve the experimental administration of abused stimulants such as cocaine [71]. Eliminating or substantially reducing drug taking in nontreatment seeking, cocaine-dependent participants with a pharmacological adjunct, therefore, may be especially difficult. The results of a recently published report suggest that agonist-replacement therapy is less effective in nontreatment-seeking participants [72]. In this elegantly designed experiment, the efficacy of nicotine replacement therapy (0- or 21-mg patch) was assessed in treatment- and nontreatment-seeking cigarette smokers (n = 47 and 93, respectively). Nicotine replacement therapy was chosen for study because it has demonstrated efficacy in clinical trials. A significant interaction of nicotine (0- or 21-mg patch) and treatment status (treatmentor nontreatment-seeking) was observed on the number of days abstinent during a 4-day experimental period. The 21-mg nicotine patch nearly doubled the number of days abstinent relative to the placebo in the treatment-seeking group. The 21-mg nicotine patch had very little effect relative to placebo in the nontreatment seeking group. Similar effects were observed for carbon monoxide levels.

Monoamine releasers

Amphetamines, as noted above, act as substrates for monoamine transporters and are transported into the nerve terminal where they promote the release of monoamines into the synapse by preventing the accumulation of neurotransmitter in storage vesicles and also by carrier-mediated exchange. Since cocaine and amphetamines increase extracellular monoamine levels, albeit by different mechanisms, the latter, and perhaps other monoamine releasers, may function as agonist-replacement therapies for the former.

Consistent with these biochemical data, the behavioral effects of D-amphetamine and cocaine overlap extensively [38,73]. Amphetamines and cocaine maintain self-administration and there appears to be little difference between these drugs in terms of their reinforcing effects [74–78]. In one report, for example, separate groups of rats could self-administer cocaine (0.187–3.0 mg/kg/injection) or D-amphetamine (0.47–0.75 mg/kg/injection) under a progressive-ratio schedule [76]. Under a progressive-ratio schedule, the response requirement to obtain a reinforcer (e.g., an injection of cocaine) systematically increases. The last ratio completed to obtain a reinforcer is referred to as the break point and is the dependent measure. Progressive-ratio schedules are thought to provide an index of reinforcing efficacy or ‘strength’ [79]. Cocaine and D-amphetamine did not differ in terms of break point at the doses that maintained maximal responding. The discriminative-stimulus

and subjective effects of D-amphetamine and cocaine are virtually indistinguishable [80–83]. In one preclinical experiment, for example, rats were trained to discriminate cocaine (29.4 μmol/kg) from saline [82]. After acquiring the discrimination, a range of doses of D-amphetamine and methamphetamine (0.56–5.6 μmol/kg) was tested to determine if they shared discriminative-stimulus effects with cocaine. D-amphetamine and methamphetamine dose dependently increased cocaine-appropriate responding and the two highest doses tested completely substituted (i.e., occasioned ≥80% drug-appropriate responding).

In a human laboratory experiment, five cocaine-abusing volunteers were taught to discriminate p.o. cocaine (80 mg/70 kg) from placebo [83]. After acquiring the discrimination, a range of doses of D-amphetamine (5–20 mg/70 kg) was tested to determine if they shared discriminative-stimulus effects with cocaine. D-amphetamine dose dependently increased cocaine-appropriate responding and the highest dose tested completely substituted. In another study, ten cocaine-abusing volunteers were taught to discriminate iv. cocaine (20 mg/70 kg) from placebo [80]. A range of doses of methamphetamine (5–10 mg/70 kg) was tested to determine if they shared discriminative-stimulus effects with cocaine. Methamphetamine dose dependently increased cocaine-appropriate responding. These behavioral data further suggest that amphetamine analogs might function as agonist-replacement therapies for cocaine dependence.

Preclinical drug self-administration experiments—Treating animals acutely or chronically with amphetamine congeners shifts the cocaine dose–response curve for the reinforcing effects of cocaine. Interestingly, however, the dose (i.e., low vs high) and dosing regimen (i.e., acute pretreatment vs chronic maintenance), determines the direction that the amphetamine congener shifts the cocaine dose response function. In one study, a self-administration procedure was used to assess the acute effects of D-amphetamine pretreatment on the reinforcing effects of cocaine [84]. Across the range of doses tested, cocaine (0.032–1.0 mg/kg/injection) produced an inverted U-shaped dose–effect curve (i.e., low to intermediate doses functioned as reinforcers while high doses did not). Pretreating rats with 1.8 mg/kg D-amphetamine enhanced the reinforcing effects of a low dose of cocaine (0.032 mg/kg/injection), but reduced the effects of higher cocaine doses (0.1, 0.32 and 1.0 mg/kg/injection). Pretreating rats with a high dose of D-amphetamine (3.2 mg/kg) almost completely eliminated responding for all doses of cocaine. In an earlier study, rats were allowed to self-administer a range of doses of cocaine (0.25–1 mg/kg/injection) [85]. Pretreating the rats with 1.5 mg amphetamine reduced the number of injections of each cocaine dose relative to baseline self-administration.

Chronically treating animals with D-amphetamine attenuates the reinforcing effects of cocaine under a variety of behavioral procedures in different species [60,86–91]. In one study, for example, the effects of D-amphetamine maintenance (5 mg/kg/day for 14 days) on cocaine (0.19–1.5 mg/kg/injection) self-administration were assessed in rats using a progressive-ratio schedule [86]. As expected, cocaine dose dependently increased break points prior to the implantation of D-amphetamine osmotic mini-pumps. D-amphetamine significantly decreased responding for cocaine (0.19 and 0.38 mg/kg/injection). In a series of experiments, rhesus monkeys were allowed to self-administer iv. cocaine (0–0.1 mg/kg/injection) and food pellets while maintained on placebo or D-amphetamine (0.01–0.1 mg/kg/h) or methamphetamine (0.1–0.01 mg/kg/h) [90–92]. D-amphetamine and methamphetamine robustly decreased cocaine-taking behavior, but had a more limited effect on food-maintained responding. Worth noting is that at least one dose of D-amphetamine or methamphetamine completely eliminated cocaine-taking behavior.

Human drug self-administration studies—Two human laboratory experiments directly assessed the reinforcing effects of cocaine in participants maintained on D-

amphetamine [52,93]. In the study completed in our laboratory, nine cocaine-dependent participants participated in a within-subject experiment [93]. Participants were maintained on D-amphetamine (0 and 40 mg/day) for 3–5 days. These conditions were tested in a counter-balanced fashion. During five experimental sessions under each maintenance condition, participants first sampled placebo (i.e., 4 mg intranasal cocaine) identified as Drug A. Participants then sampled a second intranasal drug dose (4, 10, 20 or 30 mg cocaine) identified as Drug B. Participants then made six discrete choices between Drug A and Drug B. All doses of cocaine were chosen significantly more than placebo during both maintenance conditions (i.e., placebo and D-amphetamine). Choice of the 20-mg dose of cocaine was significantly lower during D-amphetamine maintenance relative to when this cocaine dose was tested during placebo maintenance.

In the other study, eight participants with co-morbid cocaine and opioid dependence completed a 3-week inpatient protocol [52]. Participants were maintained on buprenorphine (8 mg/day) throughout the study and ascending doses of D-amphetamine (0, 30 and 60 mg) for 3-day blocks. After 3 days of maintenance on each D-amphetamine dose, participants sampled four drug conditions:

- Cocaine (4 mg intranasally) plus hydromorphone (0 mg, intramuscular [im.]; i.e., this is the placebo condition);
- Cocaine (100 mg intranasally) plus hydromorphone (0 mg, im.);
- Cocaine (4 mg intranasally) plus hydromorphone (24 mg, im.);
- Cocaine (100 mg intranasally) plus hydromorphone (24 mg, im.).

Later in the day, participants could respond on a progressive ratio schedule to receive the sampled drug or money ($2.00). As expected, participants responded for more doses of cocaine than placebo. Responding for cocaine was significantly reduced by maintenance on both doses of D-amphetamine. D-amphetamine did not alter responding for hydromorphone or the cocaine–hydromorphone combination.

Two studies used a multiple-choice procedure to assess the reinforcing effects of cocaine in participants maintained on D-amphetamine and placebo [52,94]. The multiple-choice procedure provides a contingency-based, but indirect, assessment of the monetary value of each dose condition [95,96]. In this procedure, volunteers make a series of discrete choices between each drug dose they received and ascending amounts of money (e.g., $0.10, 0.25, 0.50, 1.00, 2.00, 4.00, 8.00 and 16.00). After receiving each of the cocaine doses, participants randomly selected one of their previous choices during that session in a lottery. This choice (drug or money) is then presented to the subject. Data from the multiple-choice procedure are analyzed as ‘crossover point’ (i.e., the maximum dollar value at which volunteers chose drug over money). In a previous study conducted in our laboratory, participants (n = 7) completed the multiple-choice procedure for varying doses of intranasal cocaine (4 [placebo], 30, 60 mg) while maintained on ascending dose of D-amphetamine (0, 15 and 30 mg/day) [94]. Cocaine (30 and 60 mg) increased the crossover point above levels observed with placebo (i.e., 4 mg) during placebo maintenance, although this effect did not attain statistical significance. D-amphetamine tended to attenuate the effects of these cocaine doses. The multiple-choice procedure was also included in the study described above that assessed the reinforcing effects of cocaine (4 [placebo] and 100 mg) and hydromorphone (0 and 24 mg), alone and combined, in cocaine and opioid dependent participants (n = 8) maintained on D-amphetamine (0, 30 and 60 mg/day) and buprenorphine (8 mg/day) [52]. Cocaine functioned as a reinforcer as evidenced by a significant increase in the crossover points during placebo maintenance. There was a reduction in the reinforcing effects of

cocaine as function of the D-amphetamine maintenance dose as depicted graphically, but this effect did not attain statistical significance.

Human subjective-effects studies—A previous study conducted in our laboratory measured subjective responses to intranasal cocaine (4 [placebo], 30, 60 mg) in participants maintained on D-amphetamine (0, 15 and 30 mg/day) [94]. Participants (n = 7) were administered these doses of intranasal cocaine in ascending order within a single session after 3–5 days of D-amphetamine maintenance (0, 15 and 30 mg/day) [94]. Cocaine produced prototypical subjective effects (i.e., increased ratings of Good Effects, High, Like Drug Rush and Willing to Pay For). D-amphetamine maintenance significantly attenuated the effects of cocaine on ratings of Good Effects and High. Both doses of cocaine also increased scores significantly above placebo (4 mg) levels on a stimulant-sensitive adjective-rating scale during maintenance on 0 mg/day day amphetamine. Scores on this scale were significantly lower following the administration of cocaine (30 and 60 mg) during maintenance on both doses of D-amphetamine relative to when these cocaine doses were tested during placebo maintenance.

As part of the drug self-administration experiments described above, subjective responses to cocaine were also measured [52,93]. The results of these studies are mixed. In the study conducted in our lab, we assessed subjective responses to intranasal cocaine (4, 10, 20 and 30 mg) in participants maintained on D-amphetamine (40 mg/day) or placebo [93]. As expected, cocaine dose dependently increased ratings of Good Effects, Like Drug, and Willing to Take Again under both maintenance conditions. D-amphetamine maintenance did not significantly alter the effects of cocaine on these measures. In the other study, subjective responses to cocaine (4 and 100 mg) and hydromorphone (0 and 24 mg), alone and combined, were assessed in co-morbid cocaine- and opioid-dependent participants maintained on ascending doses of D-amphetamine (0, 30 and 60 mg) [52]. As expected, 100 mg of cocaine significantly increased ratings of Any Effect, Good Effects, High, Drug Liking, Stimulated, and Want Drug Again relative to placebo cocaine (i.e., 4 mg). Maintenance on D-amphetamine (30 or 60 mg/day) significantly attenuated the effects of cocaine on each of these measures except High. Cocaine also increased scores on the morphine benzedrine group, amphetamine and lysergic acid diethylamide scales of the Addiction Research Center Inventory. D-amphetamine maintenance did not alter these effects of cocaine.

Clinical trials—While the preclinical and human laboratory experiments reviewed above suggest amphetamine analogs may be effective pharmacotherapies for managing cocaine dependence, double-blind, placebo-controlled, randomized clinical trials are the gold standard. The results of the initial clinical trials suggest that amphetamine congeners are effective for treating cocaine dependence [20,97,98]. In the seminal trial, for example, cocaine-dependent patients (n = 128) were randomly assigned to receive D-amphetamine (15 or 30 mg/day; n = 26 and 28, respectively) or placebo (n = 40) for 25 weeks [97]. During the fifth week, the D-amphetamine dose was doubled. Patients maintained on D-amphetamine (30/60 mg/day) used significantly less cocaine during the trial than patients maintained on either the lower D-amphetamine dose (15/30 mg/day) or placebo as determined by benzoylecgonine-free urines. These investigators have replicated this finding and so have others [20,98].

In another trial, cocaine dependent patients were randomly assigned to receive immediate-release methamphetamine (5 mg [p.o.], six-times/day; n = 30) or sustained-release methamphetamine (30 mg [p.o.] in the morning and placebo five-times/day; n = 25) or placebo (six-times/day [p.o.], n = 27) for 8 weeks [26]. p.o. sustained-release methamphetamine dramatically reduced the proportion of cocaine-positive urine samples in

all randomized patients (i.e., intent-to-treat analysis) and in patients that completed the trial. The percent of cocaine-positive urine samples was approximately 10, 55 and 50% in patients assigned to p.o. sustained-released methamphetamine, p.o. immediate-release methamphetamine and placebo, respectively, during the final week of the trial. This reduction in cocaine use with sustained-release methamphetamine is comparable to that observed with the most effective behavioral treatment for cocaine dependence, contingency management [99] and far exceeds what has been observed with other pharmacotherapies. There were no differences in retention across the three groups. p.o. methamphetamine was safe and well tolerated. Only a single patient was discontinued due to side effects attributed to the study medications. Not surprisingly, compliance with a six capsules/day dosing regimen was low. However, most patients ingested the first daily capsule. Thus, the greater efficacy with sustained-versus immediate-release methamphetamine may be attributed to functionally different doses (i.e., 5 vs 30 mg). This 'proof-of-concept' trial with a potent amphetamine analog with a broad spectrum of action (i.e., enhances activity in dopamine, serotonin and norepinephrine systems) provides strong evidence for the continued development of agonist-like medications for managing cocaine dependence.

Summary—The pharmacological and behavioral effects of amphetamines and cocaine overlap extensively, suggesting the former might function as an agonist-replacement therapy for cocaine dependence. The results of preclinical studies suggest that chronically treating animals with D-amphetamine attenuates the reinforcing effects of cocaine. Similarly, the results of laboratory studies suggest that pretreating humans with D-amphetamine attenuates the reinforcing and subjective effects of cocaine. Finally, the results of recent clinical trials have consistently shown that D-amphetamine reduces cocaine use. This translational literature clearly supports the continued development of monoamine releasers such as D-amphetamine for cocaine dependence.

More research is needed, however, to elucidate the optimal conditions (e.g., dose) under which agonist-replacements therapies, such as D-amphetamine, are effective. Treatment retention and compliance remains discouragingly low even in patients treated with p.o. D-amphetamine or methamphetamine [20,25,26,97]

Summary of dopamine uptake inhibitors & releasers

The literature reviewed above supports the utility of dopamine releasers, and, to a lesser extent, uptake inhibitors, as agonist-replacement strategies for managing cocaine dependence. However, these medications have significant abuse and diversion potential [31,32]. Clinicians are reluctant to use monoamine releasers transport blockers to manage cocaine dependence because of these problems. The viability of the agonist-replacement approach for cocaine dependence may hinge on identifying novel agonist therapies that have less abuse and diversion potential.

Alternative agonist-replacement therapies for cocaine dependence

Considerable efforts have been directed towards identifying putative agonists replacement therapies that are devoid of abuse and diversion potential. Two compounds that have weak agonist-like effects and limited abuse potential, bupropion and modafinil, have received the most scientific attention as putative replacement therapies for cocaine.

Bupropion

Bupropion (Wellbutrin®, Zyban®) is an effective antidepressant that is also used as an adjunct in smoking cessation [100,101]. Bupropion is a weak dopamine indirect agonist that binds to the dopamine transporter and increases extracellular DA levels in the nucleus

accumbens [102,103]. The behavioral effects of bupropion overlap to some extent with those of prototypical stimulants. Bupropion substitutes for cocaine in **drug-discrimination** studies [104] and is self-administered by laboratory animals [51]. Human laboratory studies have shown that bupropion has minimal abuse potential [31,105–107].

These neuropharmacological and behavioral data suggest bupropion may be well suited as an agonist-replacement therapy for cocaine dependence. We are not aware of any preclinical reports that assessed the efficacy of bupropion as a potential agonist-replacement therapy for cocaine dependence. Human laboratory experiments and clinical trials have assessed the efficacy of bupropion as a putative agonist-replacement therapy for cocaine dependence, however. The results of these studies have dampened enthusiasm for the continued study of bupropion as an agonist-replacement therapy for cocaine dependence.

Human laboratory studies—Two human laboratory experiments determined the putative efficacy of bupropion as an agonist-replacement therapy for cocaine dependence [108,109]. One experiment determined the subjective effects of intranasal cocaine (0, 50 and 100 mg/70 kg) in volunteers (n = 7) maintained on 150 and 300 mg/day bupropion [108]. The cocaine dose–response curve was determined before participants completed the bupropion conditions. During this session, cocaine produced prototypical stimulant-like subjective effects (e.g., increased ratings of Drug Liking). Bupropion maintenance did not alter the subjective effects of cocaine. In a recent study in our laboratory, cocaine-using adults (n = 8) completed nine experimental sessions in which they were first pretreated with 0, 100 or 200 mg p.o. immediate-release bupropion [109]. 90 min later they sampled an intranasal cocaine dose (4 [placebo], 15 or 45 mg) and made six choices between that dose and an alternative reinforcer ($0.25), available on concurrent progressive ratio schedules. The highest dose of cocaine functioned as a reinforcer following placebo pretreatment. Bupropion significantly attenuated the reinforcing effects, although this effect was modest in magnitude (i.e., less than one choice). By contrast, bupropion pretreatment enhanced some subjective effects of cocaine (e.g., Good Effects).

Clinical trials—To our knowledge, five double-blind, placebo-controlled trials that explicitly assessed the efficacy of bupropion for managing cocaine dependence [110–114]. While the initial trial showed bupropion reduced cocaine use in methadone-maintained patients [111], the majority of subsequent trials have failed to demonstrate a robust effect of bupropion for managing cocaine dependence [110,112,114]. In the most recent trial, for example, cocaine-dependent patients were randomly assigned to placebo (n = 33) or 300 mg/day bupropion (n = 37) for 16 weeks. The groups did not differ significantly on any outcome measure, including drug urine results.

One other trial has demonstrated limited efficacy with bupropion [113]. In this study, participants (n = 106) were randomized to one of four conditions for 25 weeks:

- Bupropion (0 mg/day) plus contingency management;
- Bupropion (300 mg/day) plus contingency management;
- Bupropion (0 mg/day) plus voucher control;
- Bupropion (300 mg/day) plus voucher control.

Participants assigned to either of the contingency management conditions received monetary-based vouchers contingent on providing drug-free urine samples. Participants assigned to either of the voucher-control conditions received a $3 voucher for providing a urine sample independent of the results of the urine drug tests. Bupropion reduced cocaine use, but only when combined with contingency management. These findings suggest

bupropion may be effective under a limited set of conditions or in combination with other treatments.

Modafinil

Modafinil (Provigil®) is a novel stimulant indicated in the treatment of narcolepsy or excessive daytime sleepiness [115–118]. The neuropharmacological mechanisms that mediate the stimulant effects of modafinil are not completely understood, but some evidence suggests that it may weakly bind to the dopamine transporter and block reuptake [119–122]. One study, for example, used positron emission tomography to demonstrate that modafinil blocks dopamine transporters and increases extracellular dopamine levels in humans [121].

Consistent with these biochemical data, the behavioral effects of modafinil overlap to some extent with those of prototypical stimulants [123–126]. As an example, in one study, the discriminative-stimulus effects of a range of doses of modafinil (3.2–32 mg/kg) was determined in rhesus monkeys (n = 7) trained to discriminate 0.18 or 0.4 mg/kg cocaine [125]. Modafinil substituted for cocaine in six of seven monkeys. In a previous drug-discrimination study conducted in our laboratory, a range of doses of p.o. cocaine (50, 100 and 150 mg), modafinil (200, 400 and 600 mg) and placebo was tested in six participants with recent histories of cocaine use that had learned to discriminate 150 mg cocaine [127]. The two highest doses of modafinil partially substituted (i.e., ~46 and 54% drug-appropriate responding, respectively) for cocaine.

While modafinil shares some pharmacological and behavioral effects with prototypical stimulants, it appears to have less abuse potential [128–131]. Modafinil did not produce a conditioned-place preference (32–256 mg/kg), nor did it maintain self-administration (0.28–1.7 mg/kg/injection) [85,124]. In a previous study in our laboratory, modafinil (0–600 mg) was nearly devoid of positive subjective effects [126]. A recent human laboratory study showed that modafinil (200–600 mg) did not function as a reinforcer using a choice procedure [132].

Overall, the neuropharmacological and behavioral effects of modafinil overlap to some extent with those of prototypical stimulants that are effective agonist-replacement therapies for cocaine dependence. Importantly, modafinil appears to have minimal abuse potential. These characteristics have prompted considerable interest in testing modafinil as a putative agonist-replacement therapy for cocaine dependence.

Preclinical experiments—In a recent report, rhesus monkeys (n = 4) were trained to respond for cocaine (0.001–0.1 mg/kg/injection) or food under a second-order schedule of reinforcement [125]. As expected, cocaine produced an inverted U-shaped dose–response curve maximal responding maintained by 0.003 and 0.01 mg/kg/injection. Modafinil maintenance (32 mg/kg/day) significantly attenuated the reinforcing effects of both of these doses of cocaine, but did not affect responding maintained by higher doses of cocaine. Modafinil did not affect responding maintained by food. These findings are discordant with those from an earlier study that found that acute modafinil (32–128 mg/kg) pretreatment did not alter cocaine (0.25–1 mg/kg/injection) self-administration in rats [85]. The reason for this discrepancy is unknown but could be due to the modafinil dosing regimen (i.e., chronic vs acute).

Human laboratory studies—The results of human laboratory studies suggest modafinil attenuates the reinforcing and subjective effects of cocaine [133–135]. In one study, the reinforcing effects of smoked cocaine (0, 12, 25 and 50 mg) were assessed in participants (n = 8) maintained on modafinil (0, 200 and 400 mg/day) [134]. These doses of smoked cocaine were tested on separate days. Participants first sampled the available cocaine dose

and then made five choices between another drug dose and $5.00. As expected, cocaine choices increased as a function of dose. Cocaine choices were decreased during maintenance on both doses of modafinil. Maintenance on modafinil also attenuated some of the positive subjective effects of smoked cocaine.

Clinical trials—The behavioral neuropharmacological profile of modafinil, along with the promising results of preclinical experiments and human laboratory experiments generated hope that modafinil might be an effective agonist-replacement therapy for managing cocaine dependence. The results of the initial clinical trial further fueled this hope [136]. In this trial, cocaine-dependent patients were randomly assigned to receive 400 mg/day modafinil (n = 30) or placebo (n = 32) for 8 weeks. The modafinil-treated patients provided significantly more benzoylecgonine-free urine samples than the placebo-treated patients. The authors concluded that the efficacy of modafinil needed to be determined in a larger sample.

A 12-week multi-site trial compared placebo (n = 72) and modafinil (200 [n = 69] and 400 mg [n = 68]) [137]. The initial analysis showed little difference between placebo and either dose of modafinil in terms of average weekly percent of cocaine non-use days across the trial. *Post hoc* analyses, however, showed that modafinil increased the average weekly percent of cocaine non-use days in participants that did not have a history of alcohol dependence. Analysis of secondary outcome measures showed that 200-mg modafinil increased the maximum number of consecutive non-use days for cocaine and reduced craving. These data suggest that modafinil may be effective only in a subset of cocaine-dependent patients.

Summary of bupropion & modafinil

Two compounds that have weak agonist-like effects, bupropion and modafinil, have received considerable scientific attention as putative replacement therapies for cocaine. While both of these compounds have desirable pharmacological characteristics that might make their use as agonist-replacement therapies more viable, they are effective under a limited set of conditions. Bupropion, for example, is only effective when combined with contingency management. Modafinil, on the other hand, is only effective in a subset of cocaine-dependent patients (i.e., no history of alcohol dependence). The clinical use of bupropion and modafinil is clearly warranted when combined with an intense behavioral therapy or in less dependent patients. However, novel strategies are needed to enhance the efficacy of bupropion and modafinil for managing cocaine dependence.

Future directions for agonist-replacement therapies for managing cocaine dependence: novel compounds & formulations

While weak agonists therapies are effective when combined with other therapies or for a subset of cocaine-dependent patients, treating those that are severely dependent remains a challenge. As reviewed above, a potent amphetamine analog (i.e., methamphetamine) with a broad spectrum of action (i.e., promotes release of dopamine, serotonin and norepinephrine) robustly decreased drug use in a sample of cocaine-dependent patients. The use of methamphetamine to manage cocaine dependence will likely never gain widespread acceptance. Innovative strategies are needed to promote the acceptance of potent amphetamine analogs as agonist-replacement therapies for cocaine dependence. Below, we propose two possible strategies: novel compounds and prodrugs.

Novel compounds

Preclinical experiments, human laboratory studies and clinical trials clearly demonstrate that agonist-replacement therapy is a viable strategy for managing cocaine dependence. Over the

past two decades, medicinal chemists have synthesized several compounds in an attempt to identify an effective, yet acceptable, agonist-replacement therapy for cocaine dependence. Some of these compounds are highly selective for the dopamine transporter (i.e., 3-phenyltropane analogs of cocaine [RTI-336]), while others are selective for promoting dopamine release (i.e., benzylpiperazine; (+)phenmetrazine; and 4-benzylpiperidine). Here, we briefly review the existing literature regarding novel transport blockers and dopamine releasers that may be promising agonist-replacement alternatives for managing cocaine dependence. These compounds are still in preclinical development and have not yet been tested in human laboratory studies or clinical trials to determine their efficacy for managing cocaine dependence. Thus, this discussion is not intended to be exhaustive.

Novel dopamine transport blockers—Based on the premise that an effective agonist replacement should have some cocaine-like effects, but less abuse potential, medicinal chemists have successfully synthesized several novel dopamine transporter blockers [138–142]. RTI-336, 3β-(4-chlorophenyl)-2β-[3-(4'-methylphenyl)isoxazol-5-yl]tropane, has been proposed as the lead candidate to move forward in development. RTI-336 has a high affinity for the dopamine transporter (IC_{50} = 4.1 nM) [141]. RTI-336 binds the dopamine transporter more selectively than either the norepinephrine or serotonin transporter (i.e., ~420- and 1400-fold, respectively) [139]. The behavioral effects of RTI-336 onset more slowly than several other novel dopamine transport blockers, perhaps due to slower penetration of the CNS [141,143,144].

Consistent with these neurochemical data, the behavioral effects of RTI-336 overlap with those of cocaine. In drug-discrimination studies, RTI-336 substitutes for cocaine in animals trained to discriminate cocaine (10 mg/kg) [139,140,142]. Similar to cocaine, RTI-336 functions as a reinforcer and maintains self-administration [88,143]. However, RTI-336 is not as reinforcing as cocaine [88,145]. In the most recent study, for example, rhesus monkeys (n = 4) were allowed to self-administer varying doses of cocaine (0.003–0.3 mg/kg/injection), RTI-336 (0.003–0.1 mg/kg) or saline under a progressive-ratio schedule of drug reinforcement [88]. Statistical analysis of the group data showed that the reinforcing strength of RTI-336 was significantly lower than that of cocaine.

Perhaps most importantly, RTI-336 maintenance reduces cocaine self-administration in different species under a variety of behavioral arrangements [141,145,146]. In one study, rhesus monkeys (n = 4) were allowed to self-administer cocaine (0.1 or 0.3 mg/kg/injection) under a multiple second-order schedule of drug or food delivery [145]. These doses of cocaine maintained high rates of responding. RTI-336 (0.3–1.7 mg/kg) dose dependently decreased the reinforcing effects of both of these cocaine doses and food.

In summary, RTI-336 is a highly selective dopamine transport blocker that produces cocaine-like discriminative-stimulus effects. The behavioral effects of RTI-336 onset more slowly than several other novel dopamine transport blockers, perhaps due to slower penetration of the CNS. RTI-336 is thus a less potent reinforcer than cocaine. RTI-336 reduces cocaine self-administration in different species under a variety of behavioral arrangements. Collectively, the behavioral pharmacologic characteristics of RTI-336 suggest it may be a viable agonist-replacement therapy for managing cocaine dependence.

Novel dopamine releasers—As described above, there is translational evidence to suggest that the monoamine releasers (i.e., amphetamine derivatives) are effective agonist-replacement therapies for managing cocaine dependence. However, amphetamines have abuse and diversion potential. Recent research suggests that the abuse potential of dopamine releasers can be reduced via simultaneous release of serotonin [147,148]. Based on this premise, some theoreticians have argued that an effective agonist-replacement therapy with

reduced abuse potential can be designed by altering the potency ratios to promote serotonin and dopamine release [149].

Several compounds with varying potency ratios to promote serotonin and dopamine release have been tested in preclinical experiments to determine the viability of this strategy to identify a more acceptable agonist-replacement therapy [92,149,150]. In the earliest study, the investigators painstakingly screened over 350 compounds to determine potency ratios to promote serotonin and dopamine release [149]. These efforts identified 1-napthyl-2-aminopropane (PAL-287) as the most promising candidate. PAL-287 is a nonamphetamine that is approximately equipotent for promoting serotonin and dopamine release. Subsequent experimentation suggests that the pharmacological profile of PAL-287, or similar compounds, is well suited for its use as an agonist-replacement therapy [92,149]. The psychomotor stimulant effects of the compound are less than those of amphetamine. PAL-287 produces cocaine-like discriminative-stimulus effects in monkeys, but does not maintain self-administration. Chronic PAL-287 maintenance (0.1–1.0 mg/kg/h for 7 days) completely eliminates responding for cocaine (0.01 mg/kg/injection). PAL-287 maintenance also decreased food-maintained responding, although this effect was smaller in magnitude than that observed for cocaine-maintained responding.

These investigators subsequently concluded a series of experiments to systematically determine whether the **serotonin–dopamine release ratio** (5-HT/DA ratio) systematically alters the behavioral pharmacological profile, efficacy and selectivity of various monoamine releasers [92,150]. Eight compounds were tested: fenfluramine (5-HT/DA ratio = 0.008), PAL-287 (5-HT/DA ratio = 0.27), PAL-314 (5-HT/DA ratio = 6.5), benzylpiperazine (5-HT/DA ratio = 20), methamphetamine (5-HT/DA ratio = 31), (+)phenmetrazine (5-HT/DA ratio = 37), 4-benzylpiperidine (5-HT/DA ratio = 48) and PAL-353 (5-HT/DA ratio = 80). Each of the monoamine releasers produced cocaine-like discriminative-stimulus effects. Each of these compounds, with the exception of PAL-314, decreased responding for cocaine (0.01 mg/kg/injection). Most of the compounds also reduced food-maintained responding. The most selective reduction in cocaine-maintained responding was observed with methamphetamine and (+)phenmetrazine. The authors concluded compounds with intermediate 5-HT/DA ratio (i.e., 30–40) might be the most effective agonist-replacement therapies for managing cocaine dependence.

In summary, several monoamine releasers, most notably, methamphetamine and (+) phenmetrazine, selectively reduced the reinforcing effects of cocaine. As reviewed above, p.o. methamphetamine maintenance produced a striking reduction in cocaine use in a single clinical trial [26]. In fact, this reduction in cocaine use is comparable to that observed with the most effective behavioral treatment for cocaine dependence, contingency management [99], and far exceeds what has been observed with other pharmacotherapies. While methamphetamine will never gain widespread acceptance as an agonist-replacement therapy for cocaine, these data provide compelling evidence for the notion that the 5-HT/DA ratio may be an important determinant of the efficacy and selectivity of monoamine releasers as agonist-replacement therapies. Another compound, (+)phenmetrazine, was equally effective and selective for reducing the reinforcing effects of cocaine. While phenmetrazine is no longer available commercially, below we discuss its potential use as an agonist-replacement therapy in the context of prodrugs.

Prodrugs

Rate of onset is a critical determinant of the magnitude of the abuse-related effects of stimulant drugs. The abuse-related effects of agonist-replacement therapies (i.e., stimulants) can be reduced by slowing the rate of onset of the drug effects via the use of sustained-release formulations [151,152]. In a previous study conducted in our laboratory, for

example, the acute subjective effects of p.o. administered sustained-release methylphenidate (20 and 40 mg), immediate-release methylphenidate (20 and 40 mg), and placebo were assessed in ten participants [152]. As expected, immediate-release methylphenidate produced stimulant-like subjective effects (e.g., increased ratings of Good Effects) that generally varied as a function of dose and time. Sustained-release methylphenidate, by contrast, produced transient effects on these measures that were smaller in magnitude than those observed with the immediate-release doses. These results suggest that sustained-release formulations of stimulants have less abuse potential than immediate-release preparations. However, crushing or pulverizing the tablet circumvents the sustained-release properties of these formulations.

Prodrugs are not generally active themselves and require first-pass metabolism in the gastrointestinal tract to produce the active compound in the body. As prodrugs require first-pass metabolism to create the active compound, the onset of the effects of the active drug is slowed. This critical aspect of a stimulant prodrug, reduced abuse and diversion potential due to slower rate of onset, will likely make use of these compounds more attractive candidate medications while maintaining the important aspects of the agonist-replacement strategy. Here, we review the extant literature regarding two prodrugs, lisdexamfetamine and phendimetrazine, that are promising agonist-replacement alternatives for managing cocaine dependence.

Lisdexamfetamine—Lisdexamfetamine (Vyvanse®), a recently approved prodrug for D-amphetamine, is indicated for treating ADHD. After p.o. administration, lisdexamfetamine is rapidly absorbed in the gastrointestinal tract and converted to D-amphetamine, which reaches peak plasma levels approximately 3 h after administration [153]. As described above, the results of preclinical experiments, human laboratory studies and clinical trials suggest D-amphetamine is effective for cocaine dependence. When administered chronically to humans, steady-state concentrations of D-amphetamine are reached after 5 days of maintenance, with little to no accumulation of lisdexamfetamine [154]. Recent human laboratory studies have demonstrated that both p.o. and iv. administered doses of lisdexamfetamine have minimal abuse potential [155,156]. In one study, 50 and 100 mg of p.o. lisdexamfetamine failed to increase subjective ratings indicative of abuse potential although a supratherapeutic dose, 150 mg, produced ratings of Drug Liking similar to those observed with 40 mg D-amphetamine [156].

Because lisdexamfetamine has reduced abuse and diversion potential, it may be a more viable agonist-replacement therapy for managing cocaine dependence. A clinical trial is being conducted to determine the efficacy of lisdexafetamine for cocaine dependence (NCT00958282).

Phendimetrazine—Phenmetrazine (3-methyl-2-phenylmorpholine) was developed as an appetite suppressant. As reviewed above, phenmetrazine maintenance completely eliminated cocaine-taking behavior but had minimal effect on food-maintained responding [150]. While these data suggest that phenmetrazine might be an effective agonist-replacement therapy for cocaine dependence, it was removed from the market due to high abuse and dependence potential.

Phendimetrazine (Bontril®), a prodrug of phenmetrazine, is indicated for treating obesity. After p.o. administration, phendimetrazine is converted to phenmetrazine. In animal studies, conversion to phenmetrazine is largely responsible for the neuropharmacological effects observed following phendimetrazine administration [157]. Data from nonhuman and human behavioral pharmacology studies suggest that phendimetrazine may be an ideal agonist-replacement therapy for cocaine dependence. Phendimetrazine produces discriminative

effects similar to amphetamine [158,159]. Importantly, unlike phenmetrazine, phendimetrazine only maintains self-administration under limited conditions [160,161]. Thus, phendimetrazine produces some stimulant-like drug effects, but it has low abuse potential. We do not know of any human laboratory studies or clinical trials in which phendimetrazine was tested as a pharmacotherapy for cocaine dependence. Such research is clearly warranted.

Drug-combination therapy

As noted above, novel strategies are needed to enhance the efficacy of weak dopamine agonists. Bupropion and modafinil are effective for managing cocaine dependence, but only under a limited set of conditions. Combining bupropion and modafinil is one such novel and innovative approach. Drug-combination therapy has been an effective strategy for managing other psychiatric conditions, such as depression [45,162,163]. Drug-combination therapy might also be effective for managing cocaine dependence.

The results of a series of preclinical studies elegantly demonstrate that the combination of low doses of two different drugs is an effective strategy to manage cocaine dependence and minimize the untoward effects of the constituent compounds [164–166]. In those studies, high doses of benzodiazepines (alprazolam, chlordiazepoxide and oxazepam) attenuated the reinforcing effects of cocaine. The rationale for testing benzodiazepines is that they decrease plasma corticosterone levels and cocaine-induced increases in corticosterone, thereby addressing the stress response associated with cocaine abstinence and cue exposure [167–169]. Those investigators have also shown that metyrapone, a corticosterone synthesis inhibitor, decreased cocaine self-administration [170]. The clinical use of high doses of benzodiazepines and corticosterone synthesis inhibitors to manage cocaine dependence is problematic because of side effects. Benzodiazepines have abuse potential, dependence liability and impair performance [171–175]. Corticosterone synthesis inhibitors can cause adrenal insufficiency.

To circumvent the side effects associated with high doses of the constituent drugs, these investigators tested the hypothesis that combining low doses of a benzodiazepine and metyrapone would significantly attenuate the reinforcing effects of a range of doses of cocaine (0.125, 0.25 and 0.5 mg/kg/injection) [166]. Rats were given the opportunity to self-administer cocaine following pretreatment with oxazepam (10–20 mg/kg) or metyrapone (50–100 mg/kg). High doses of oxazepam and metyrapone alone reduced cocaine self-administration to levels similar to those observed during extinction. When doses of oxazepam and metyrapone that were ineffective when tested alone were combined, cocaine self-administration was again reduced to levels similar to those observed during extinction. The authors concluded that because the two drugs acted through distinct mechanisms that the incidence of side effects would be reduced.

The results of a small clinical trial are consistent with these preclinical findings and suggest that oxazepam–metyrapone combinations may be effective for managing cocaine dependence [176]. This double-blind, placebo-controlled study assessed the safety and efficacy of combinations of the cortisol synthesis inhibitor metyrapone, and the benzodiazepine oxazepam, in 45 cocaine-dependent patients. Patients were randomly assigned to metyrapone (500 mg/day) plus oxazepam (20 mg/day); metyrapone (1500 mg/day) plus oxazepam (20 mg/day); or placebo for 6 weeks. The outcome measures were cocaine craving and cocaine use as determined by drug urine tests. The metyrapone–oxazepam combinations were well tolerated and produced significant reductions in cocaine craving and cocaine use at several time points when controlling for baseline scores. These findings suggest drug-combination therapy may be an effective strategy for managing cocaine dependence. Future research should determine if combining weak dopamine

agonists, such as bupropion and modafinil, might be more effective than the constituent drugs for managing cocaine dependence.

Concluding remarks

Cocaine dependence is an unrelenting public-health concern. A widely effective medication has not been identified for cocaine dependence even though it has been a priority for the National Institute on Drug Abuse for nearly three decades [13,14,21]. The translational literature reviewed above suggests that agonist-replacement therapy, especially monoamine releasers, may be a viable strategy for managing cocaine dependence because:

- Maintaining nonhuman laboratory animals on monoamine releasers decreases the reinforcing effects of cocaine under a variety of behavioral procedures;
- Maintaining nontreatment-seeking human research participants on monoamine releasers decreases the reinforcing and positive subjective effects of cocaine;
- Amphetamine analogs significantly reduce cocaine use in clinical trials. The translational literature with dopamine transport blockers is more mixed.

We would like to emphasize that this review of the translational literature is not intended to encourage the widespread or long-term use of agonist replacement therapies for the management of cocaine dependence. As repeatedly stated throughout this review, researchers recognize the problems inherent to agonist-replacement therapy (i.e., abuse and diversion potential). However, until a more acceptable and effective medication is available, there are few options available to clinicians to manage cocaine dependence. Extended-release formulations of amphetamines are available and should be considered until effective alternatives are identified. This is especially true for the more severely dependent.

This translational review is, instead, intended to promote both clinical and basic science research. The robust efficacy of some agonist-replacement therapies (e.g., methamphetamine) clearly indicates that cocaine-taking behavior is amenable to pharmacological manipulation. At the very least, agonist-replacement therapy can be used as a tool to refine and improve the experimental methods used to determine the efficacy of novel compounds for managing cocaine dependence. From a clinical perspective, an agonist-replacement therapy (e.g., methamphetamine) can be used as a standard to which novel compounds can be compared. From a basic science perspective, agonist-replacement therapy can be used as a tool to identify laboratory procedures that best predict the clinical efficacy of novel agonist-replacement therapies. Using a ‘bedside-to-bench’ or ‘reverse engineering’ strategy for determining the predictive validity of laboratory procedures is important because these studies can be conducted more rapidly and efficiently than clinical trials. Human laboratory procedures might also identify the optimal conditions under which an agonist-replacement therapy might be effective (e.g., dose; initiate abstinence or prevent relapse). The use of agonist-replacement therapy as a tool will, eventually, result in identifying an effective pharmacotherapy for cocaine dependence that is acceptable to clinicians.

Future perspective

The controversy surrounding the use of available agonist-replacement medications for cocaine dependence indicates that any future acceptable agonist-replacement therapy will have to meet very specific criteria, namely, being safe, effectively reducing cocaine use and possessing little to no abuse potential. These significant challenges do not mean that this strategy should be abandoned. In fact, given the promising data reviewed above, the field should re-double its efforts in this area. Over the next 5–10 years, we envision that progress

will have been made in development of acceptable agonist-replacement therapy for cocaine dependence, particularly with the novel compounds identified above (e.g., RTI-336 and PAL-287) or with stimulant prodrugs, such as lisdexamfetamine or phendimetrazine. It is also likely that promising combination therapies will have been identified. A long timeline is necessary for full approval of pharmacotherapies for managing drug use disorders. Approval of buprenorphine for managing opioid took nearly 20 years. We envision that the most promising candidates will only be entering Phase III trials to demonstrate widespread efficacy within this time frame.

Executive summary

Agonist replacement therapies for cocaine dependence

- A translational literature exists to suggest that agonist-replacement therapies, specifically monoamine releasers, are effective in managing cocaine use disorders.
- Available agonist-replacement therapies have considerable abuse potential, so other agonist-type options must be identified and tested.

Alternative agonist-replacement therapies for cocaine dependence

- Alternative agonist-replacement therapies (i.e., bupropion and modafinil) that have been tested have only demonstrated limited efficacy in managing cocaine use disorders.

Future directions for agonist-replacement therapies for managing cocaine dependence: novel compounds & formulations

- Preclinical research has shown that novel compounds or drug combinations show promise for managing cocaine use disorders.
- These compounds should be evaluated in the human laboratory and in clinical trials.

Concluding remarks

- Given that cocaine use disorders represent a significant public health concern, pharmacotherapies are needed to reduce cocaine use.
- Agonist replacement therapies have demonstrated efficacy for reducing cocaine use, but available compounds are not widely used due to significant abuse potential.
- Existing agonist-replacement medications should be seen as tools for developing other medications to manage cocaine use disorders.

Key Terms

Agonist-replacement therapy	Use of a medication with similar effects to those of a drug of abuse to manage or treat drug dependence. Examples include methadone for opioid use or nicotine patches/gum for smoking.
Subjective drug effects	Interoceptive effects produced by drugs. These effects are measured in humans with questionnaires regarding the effects of an administered drug.

Drug self-administration	An experimental arrangement in which an organism is allowed to take doses of a drug. This measure is the gold standard in preclinical research for demonstrating abuse potential and has good predictive validity for the efficacy of pharmacotherapies.
Drug discrimination	An experimental arrangement in which an organism is taught to respond differentially in the presence or absence of a drug. This arrangement is pharmacologically selective and specific.
Serotonin–dopamine release ratio	A ratio indicating the ability of a monoamine releaser to promote serotonin release relative to dopamine release. It is thought that a moderate release ratio indicates a potential pharmacotherapy will be effective for managing cocaine use disorders.

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