Published in final edited form as:

Curr Pharm Des. 2013 ; 19(40): 7026–7035.

Agonist Replacement for Stimulant Dependence: A Review of Clinical Research

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Abstract

Stimulant use disorders are an unrelenting public health concern worldwide. Agonist replacement therapy is among the most effective strategies for managing substance use disorders including nicotine and opioid dependence. The present paper reviewed clinical data from human laboratory self-administration studies and clinical trials to determine whether agonist replacement therapy is a viable strategy for managing cocaine and/or amphetamine use disorders. The extant literature suggests that agonist replacement therapy may be effective for managing stimulant use disorders, however, the clinical selection of an agonist replacement medication likely needs to be based on the pharmacological mechanism of the medication and the stimulant abused by patients. Specifically, dopamine releasers appear most effective for reducing cocaine use whereas dopamine reuptake inhibitors appear most effective for reducing amphetamine use.

Keywords

Cocaine; Methamphetamine; Agonist Replacement Therapy; Drug Self-Administration; Clinical Trial; Dopamine Releaser; Dopamine Reuptake Inhibitor

Stimulant use disorders are an unrelenting public health concern worldwide. Data from the National Survey on Drug Use and Health indicate that approximately 1.5 million Americans over 12 years of age report current (i.e., past month) cocaine use, making cocaine the most widely used stimulant in the United States [1]. That same survey indicated that approximately 353,000 Americans report current methamphetamine use and that 1.1 million Americans report current non-medical use of prescription stimulants, including d-amphetamine and mixed amphetamine salts. In the European Union, approximately 1.5 million people report current cocaine use [2]. Past month data for amphetamine use are unavailable from that survey, but it was estimated that approximately 2 million Europeans report past year use of amphetamines. Despite prevention and intervention efforts, prevalence of stimulant use has remained relatively stable (e.g., the percentage of Americans

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Disclosure: Part of the information included in this chapter/article has been previously published in *Future Medicinal Chemistry* February 2012, Vol. 4, No. 2, Pages 245-265, DOI 10.4155/fmc.11.184 (doi:10.4155/fmc.11.184)

Conflicts of Interest: The authors declare no conflicts of interest.

reporting past month cocaine use has hovered around 1% for the past decade [1]). It is important to note that these prevalence rates likely capture both non-problematic use [see 3] and problematic stimulant use or stimulant use disorders, which lead to a host of problems (see below). The stable prevalence of overall use indicates that novel approaches are necessary to help those with problematic use who are seeking treatment to stop using.

Chronic cocaine and methamphetamine use produce a number of direct health problems like cardiovascular toxicity, malnutrition or miscarriage in pregnant women [4, 5, 6, 7, 8, 9]. Stimulant use disorders also increase risks for other health issues including smoking cigarettes, comorbid psychological disorders and acquiring and transmitting sexually transmitted infections [5, 6, 10, 11, 12]. Research that identifies promising therapies for stimulant use disorders will thus have significant public health implications beyond reducing the prevalence of illicit stimulant use and the social and legal issues associated with drug use in general [13].

Behavioral therapies are effective for reducing problematic stimulant use [e.g., 14, 15, 16, 17, 18, 19]. For example, in a seminal study, a sample of 25 patients with cocaine dependence was assigned to contingency management (n=13) or 12-step counseling (n=12) [20]. Contingency management capitalizes on the behavioral nature of drug use disorders by reinforcing abstinence from drug use (e.g., providing drug-negative urine samples) with non-drug alternatives [18]. Even when missing urine samples were counted as cocaine-positive, approximately 40% of patients assigned to contingency management were able to achieve up to 11 weeks of abstinence whereas no patients in the 12-step condition did so. Moreover, 92% of urine samples for those assigned to contingency management were cocaine negative, compared to 78% for those assigned to 12-step counseling. Similar results were obtained in a larger, more recent study that enrolled 113 patients with methamphetamine use disorders who were randomly assigned to receive contingency management plus treatment as usual (n=51) or treatment as usual (n=62) [19]. Patients assigned to contingency management achieved significantly longer periods of abstinence than those assigned to treatment as usual and more patients were able to abstain for the duration of the 12-week trial, but the groups did not differ significantly in terms of treatment retention or counseling attendance, nor did they differ at follow-up (i.e., 3 and 6 months). Given that behavioral therapies like contingency management are effective for reducing problematic stimulant use, but could be improved (e.g., in the latter study, groups did not differ at follow up; [19], identifying a pharmacological adjunct to enhance the efficacy of these treatments has been a priority for the substance abuse research community for a number of years [e.g., 21, 22, 23].

Considerable efforts have focused on identifying a “stimulant antagonist” [for reviews, see 22, 24, 25, 26]. The premise of this approach is that treating patients with an antagonist will block the desired effects of a stimulant (e.g., euphoria), thereby leading to the extinction of drug-taking and drug-seeking behavior [25]. Antagonist therapies like mecamylamine and naltrexone are somewhat effective for nicotine and opioid dependence, respectively [27, 28, 29]. Several compounds attenuated the behavioral effects of cocaine in preclinical and human laboratory studies, but none have proven effective clinically [22, 26, 30, 31, 32]. 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 [30, 33, 34]. Similar results have been found in studies testing antagonist treatments for amphetamines [35, 36, 37, 38].

An alternative approach is agonist replacement therapy. As the name implies, a pharmacologically similar agent is substituted for the stimulant of abuse [see 25, 30, 39, 40]. Agonist replacement therapies are effective for nicotine and opioid dependence [e.g., 41, 42,

43, 44]. Putative stimulant agonist replacement therapies (e.g., methylphenidate and amphetamine isomers) may increase medication adherence as they often function as positive reinforcers [45, 46]. Some clinical research has shown that adherence to agonist replacements is low [40], however, so more research needs to be done comparing adherence to agonist replacement therapies and other putative treatments.

Recent publications have provided comprehensive, translational reviews of the efficacy of agonist replacement for stimulant dependence [47, 48, 49, 50], so the purpose of this paper is to review available *clinical* outcomes to determine the viability of agonist replacement therapy for managing cocaine or methamphetamine dependence. Cocaine and methamphetamine are the drugs most commonly cited as illicitly used stimulants, however, given the many similarities between methamphetamine and other amphetamine isomers like d-amphetamine [51, 52], the review will include data from relevant studies that targeted cocaine and amphetamine isomers. The results of human laboratory studies using self-administration methodologies and clinical trials are reviewed. Human laboratory self-administration studies were selected because they have the best predictive validity, relative to other measures from the human laboratory, for the clinical efficacy of putative drug use disorder pharmacotherapies [53, 54]. Moreover, the reinforcing effects of stimulants may be the single most important behavioral determinant of their abuse. By inference, then, the ability to attenuate the reinforcing effects of cocaine or amphetamine may be a necessary characteristic of an effective pharmacotherapy for stimulant dependence [55]. Clinical trials were selected because they represent the gold standard for demonstrating medication efficacy, particularly if they are placebo-controlled, double-blind and randomized. Such placebo-controlled, double-blind, randomized trials will be the focus of the review, however, clinical trials that do not meet these criteria also are included where appropriate.

Agonist Replacement Therapies for Stimulant Dependence

An ideal agonist replacement therapy for stimulant dependence should share some pharmacological and behavioral effects with cocaine or amphetamine, but have less abuse potential. Abused stimulants produce their behavioral and physiological effects *via* interaction with monoamine transporters (dopamine, serotonin and norepinephrine) [reviewed in 56, 57, 58]. 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 presynaptic terminal, but it is not transported into the cell [59]. 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 neurotransmitters in storage vesicles and also by carrier-mediated exchange [60]. Amphetamines also usually function as transporter blockers, although they are less potent at inhibiting reuptake compared to their ability to act as transporter substrates [60]. 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 stimulant dependence. The focus of these sections is on dopamine uptake blockers and releasers because this monoamine plays a prominent role in mediating the abuse-related effects of stimulants [57, 61, 62, 63, 64]. This review is limited to those transporter blockers/reuptake inhibitors (i.e., methylphenidate and bupropion) and releasers (i.e., d-amphetamine and methamphetamine) that are available for use in humans. The review also is restricted to compounds that have clinical data available for both cocaine- and amphetamine-using populations to allow for better comparison across these two stimulants. Because many dopamine transporter blockers and releasers have abuse

potential [e.g., 45, 46], which admittedly may enhance compliance, but also likely limits their clinical utility, the available clinical data with an agonist-like drug with limited abuse potential, modafinil, also are reviewed.

Dopamine Transport Blockers for Stimulant Dependence: Methylphenidate

Methylphenidate, a piperidine derivative that blocks monoamine reuptake, is commonly prescribed for behavioral problems associated with Attention Deficit Hyperactivity Disorder (ADHD) [65, 66]. Daily doses of 10-100 mg methylphenidate are effective for managing adult ADHD (for ease of comparison across compounds and to provide a frame of reference for the clinical studies reviewed here, we have provided the oral doses used in managing adult ADHD for each putative agonist replacement medication; [67]). Methylphenidate and cocaine produce very similar effects at the dopamine transporter [59, 68, 69, 70]. For example, in humans, the regional distribution of [^{11}C] methylphenidate is almost identical to that of [^{11}C] cocaine [71]. Consistent with these neuropharmacological similarities, data from preclinical and human behavioral pharmacology studies suggest that methylphenidate and cocaine produce similar pharmacodynamic effects. Methylphenidate and cocaine function as reinforcers in laboratory animals and humans under a variety of behavioral arrangements [e.g., 72, 73]. The discriminative-stimulus and subjective effects of methylphenidate are virtually indistinguishable from those produced by cocaine [e.g., 74]. As with cocaine, data from preclinical and human behavioral pharmacology studies suggest that methylphenidate and amphetamines produce similar behavioral effects. Methylphenidate and amphetamine also function as reinforcers in laboratory animals and humans under a variety of behavioral arrangements [e.g., 45, 46]. The discriminative-stimulus and subjective effects of methylphenidate also are virtually indistinguishable from those produced by amphetamine [e.g., 52, 75]. Because there appears to be little, if any, difference between methylphenidate and cocaine/amphetamines in terms of their behavioral effects, human laboratory self-administration research and clinical trials have been conducted to determine if methylphenidate might function as an agonist replacement therapy for stimulant dependence.

Human Drug Self-Administration—We know of only one study that assessed the effects of methylphenidate on the reinforcing effects of cocaine in humans [76]. In that study, cocaine-dependent patients with co-morbid ADHD (N=7) were maintained on methylphenidate (0, 40 and 60 mg/day) [76]. 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 \$2.00 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 2 of 5 choices). We are unaware of any human laboratory studies that have tested the influence of methylphenidate on the reinforcing effects of amphetamines.

Clinical Trials—The results of the clinical trials that tested methylphenidate as a putative agonist replacement therapy for cocaine dependence are generally negative. In a seminal trial that was perhaps the very first to test the efficacy of an agonist replacement for cocaine use disorders using a double-blind, placebo-controlled, randomized design, cocaine-dependent patients (N=24) were enrolled in an 11-week study of methylphenidate [77]. 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., approximately 40%) or study retention, although the negative outcomes could be due to the

relatively low daily methylphenidate dose (e.g., the effective dose for managing ADHD is 2 to 3 times higher than that tested in this study; [78]).

Three double-blind, placebo-controlled, randomized trials tested methylphenidate as a putative agonist replacement therapy in cocaine-dependent patients with co-morbid ADHD using higher doses than those tested in the initial study described above [79, 80, 81]. Agonist replacement treatment of cocaine users with ADHD could reduce ADHD symptoms and subsequently reduce cocaine use through a number of mechanisms, including eliminating the need for self-medication of ADHD symptoms with cocaine, which may be different than what would be observed in non-co-morbid populations. In the earliest trial, patients (N=48) were randomly assigned to placebo or methylphenidate in a 12-week trial [81]. 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. The trial published in 2006 randomly assigned patients to placebo (n=33) or 40 or 80 mg of methylphenidate/day (n=32) [79]. Methylphenidate did not significantly reduce cocaine use relative to placebo. In the most recent trial, patients (N=48) were randomly assigned to placebo or methylphenidate over 14 weeks [80]. 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 clinical findings is unknown, but may be related to dose. That dose contributed to the discrepancy would be consistent with the human laboratory results in that the clinical trial that demonstrated efficacy of methylphenidate for cocaine dependence in ADHD-diagnosed cocaine users used the same dose (i.e., 60 mg/day) as that of the laboratory study with a co-morbid ADHD population [76, 80], whereas the studies that failed to demonstrate efficacy in this population used different doses [79, 81].

Two double-blind, placebo-controlled, randomized clinical trials have examined the efficacy of methylphenidate for managing amphetamine use disorders in doses comparable to those tested for co-morbid cocaine dependence and ADHD [37, 82]. The earlier study demonstrated that methylphenidate significantly reduced drug use in amphetamine-dependent patients [37]. That trial randomly assigned amphetamine-dependent patients to receive 54 mg/day slow-release methylphenidate (n=17) or placebo (n=19) for 20 weeks. Methylphenidate-treated patients were 54% less likely to provide an amphetamine-positive urine sample than those receiving placebo. In the more recent trial, amphetamine dependent adults with co-morbid ADHD (N=24) were maintained on a higher dose, 72 mg sustained-release methylphenidate, or placebo [82]. Although the groups did not differ in amphetamine-positive urine results across the 12-week trial, it is important to note that all subjects were currently abstinent from amphetamine at enrollment and overall percentage of amphetamine-positive urine results was very low (i.e., 8.6% in the placebo group and 10.6% in the methylphenidate group) indicating that a floor effect may have been in place. Taken together, the outcomes of the clinical trials would indicate that methylphenidate is effective for promoting amphetamine abstinence and also may limit relapse to amphetamine use. There also is an ongoing clinical trial evaluating the efficacy of methylphenidate for managing methamphetamine dependence (NCT01044238).

Dopamine Transport Blockers for Stimulant Dependence: Bupropion

Bupropion (Wellbutrin®, Zyban®) is an effective antidepressant that also is used as an adjunct in smoking cessation or for managing adult ADHD [67, 83, 84]. Daily doses of 100-450 mg bupropion have shown some efficacy for treating adult ADHD. Bupropion is a weak dopamine indirect agonist that binds to the dopamine transporter and increases extracellular DA levels in the nucleus accumbens [85, 86]. The behavioral effects of bupropion overlap to some extent with those of prototypical stimulants. Bupropion

substitutes for cocaine in drug-discrimination studies [87]) and is self administered by laboratory animals [88]. Bupropion also increases amphetamine-appropriate responding in drug-discrimination studies [89]. Human laboratory studies have shown that bupropion has minimal abuse potential, however [90, 91, 92, 93]. These neuropharmacological and behavioral data suggest bupropion may be well suited as an agonist replacement therapy for cocaine/amphetamine dependence.

Human Laboratory Studies—One human laboratory study has determined the reinforcing effects of cocaine in combination with bupropion. In that study, cocaine-using adults (N=8) completed nine experimental sessions in which they were first pretreated with 0, 100 or 200 mg oral immediate release bupropion. Ninety minutes later they sampled an intranasal cocaine dose (4 [placebo], 15 or 45 mg) and made 6 choices between that dose and an alternative reinforcer (US\$0.25), available on concurrent progressive ratio schedules. The highest dose of cocaine functioned as a reinforcer following placebo pretreatment. Bupropion attenuated the reinforcing effects of cocaine although this effect was modest in magnitude (i.e., bupropion reduced cocaine self-administration by less than two choices). We are unaware of any human laboratory studies that have tested the influence of bupropion on the reinforcing effects of amphetamines.

Clinical Trials—Several trials have assessed the efficacy of maximum doses of 300-400 mg/bupropion/day (i.e., doses higher than those tested in the human laboratory study) for managing cocaine dependence [95, 96, 97, 98, 99]. While the initial trial showed that bupropion reduced cocaine use in methadone-maintained patients [96], the majority of subsequent double-blind, placebo-controlled, randomized trials have failed to demonstrate an effect of bupropion for managing cocaine dependence [79, 97, 99]. In the most recent trial, for example, cocaine dependent patients were randomly assigned to placebo (n=33) or 300 mg bupropion/day (n=37) for 16 weeks. The groups did not differ significantly on any outcome measure, including drug urine results.

One other trial did demonstrate limited efficacy with bupropion [98]. In that study, participants (N=106) were randomized to one of four conditions for 25 weeks: 1) Bupropion (0 mg/day) plus contingency management; 2) Bupropion (300 mg/day) plus contingency management; 3) Bupropion (0 mg/day) plus voucher control; or 4) Bupropion (300 mg/day) plus voucher control. Bupropion reduced objectively verified cocaine use, but only when combined with contingency management. These findings suggest bupropion may be effective in combination with other treatments.

Three double-blind, placebo-controlled, randomized clinical trials have examined the utility of bupropion for the management of methamphetamine dependence [24, 100, 101]. In one trial, methamphetamine-dependent patients were randomly assigned to receive placebo (n=72) or sustained-release bupropion (150 mg BID) (n=79) [24]. The bupropion-treated patients provided fewer amphetamine-positive urine samples than the placebo-treated patients, although this effect did not attain significance according to traditional statistical standards ($p = 0.09$). Secondary analyses revealed that relative to placebo, bupropion produced a statistically significant effect in patients that reported moderate, as opposed to heavy, amphetamine use at intake. Another trial produced similar results. In that study, methamphetamine-dependent patients were randomly assigned to receive placebo (n=37) or sustained-release bupropion (150 mg BID) (n=36) [101]. Again, there was not a statistically significant effect of bupropion on methamphetamine-positive urines in the sample overall, however, secondary analyses revealed that bupropion significantly reduced drug use in patients that provided fewer methamphetamine-positive urines (i.e., 0-2) during screening than those with more positive urine samples (i.e., 3-6). Retrospective analyses have further examined the outcomes of these two trials to demonstrate how bupropion might be most

effective for managing methamphetamine dependence (e.g., for those able to achieve abstinence early in treatment; [102, 103]). The most recent trial failed to demonstrate the superiority of 300 mg bupropion/day to reduce methamphetamine use, but, due to the pilot nature of the study (i.e. it was a feasibility study in a high-risk group of men who have sex with men), it was not appropriately powered to fully assess the efficacy of bupropion or to conduct sub-analyses [100].

Summary—The pharmacological and behavioral effects of methylphenidate and stimulants overlap extensively, suggesting dopamine reuptake inhibitors might function as an agonist replacement therapy for stimulant dependence. The results reviewed above reveal that although methylphenidate reduces the reinforcing effects of cocaine in the human laboratory, it generally does not reduce cocaine use. Conversely, although no human laboratory studies have tested the efficacy of methylphenidate to alter the reinforcing effects of amphetamines, methylphenidate appears to substantially reduce amphetamine use in active amphetamine users and may prevent relapse.

Bupropion, which also inhibits dopamine reuptake, appears to have some utility in the management of stimulant use disorders. However, the efficacy of bupropion appears to be limited to when it is combined with robust behavioral treatments [i.e., 98] or administered to lighter users [i.e., 24, 101]. This reduced efficacy may be due, in part, to its weaker inhibition of dopamine reuptake than prototypical stimulants [85, 86, 104]. Taken together, these data indicate that dopamine reuptake inhibitors are more effective for managing amphetamine use disorders than cocaine use disorders.

Dopamine Releasers for Stimulant Dependence: Amphetamine Isomers

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 neurotransmitters in storage vesicles and also by carrier-mediated exchange. Although the pharmacological mechanisms by which cocaine and amphetamine increase synaptic monoamine levels differ, the behavioral effects of amphetamines and cocaine overlap extensively (for reviews see [57, 105]), particularly because there appears to be little difference between the reinforcing effects of these drugs [e.g., 106, 107, 108, 109, 110]. The discriminative-stimulus and subjective effects of d-amphetamine and cocaine also are virtually indistinguishable in two-choice procedures, although three-choice procedure studies remain to be conducted and could yield different results [89, 111, 112, 113]. Similarly, d-amphetamine and methamphetamine are structurally related and produce a similar constellation of behavioral and discriminative-stimulus effects [e.g., 52, 105, 114]. Moreover, amphetamines maintain self-administration and there appears to be little difference between the isomers in terms of their reinforcing effects [e.g., 51, 115]. These behavioral data further suggest that amphetamine analogs might function as agonist replacement therapies for cocaine/amphetamine dependence. Amphetamine doses of 5-75 mg/day are effective in managing adult ADHD [67].

Human Drug Self-Administration Studies—Two human laboratory experiments directly assessed the reinforcing effects of cocaine in participants maintained on d-amphetamine [72, 116]. In the study completed in our laboratory, nine cocaine-dependent participants participated in a within-subject experiment [116]. 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 three-week inpatient protocol [72]. Participants were maintained on buprenorphine (8 mg/day) throughout the study and ascending doses of d-amphetamine (0, 30 and 60 mg; doses lower and higher than those tested in the study in our laboratory) for 7-day blocks. After 3 days of maintenance on each d-amphetamine dose, participants sampled four drug conditions: 1) Cocaine (4 mg intranasally) plus hydromorphone (0 mg, intramuscular) (i.e., this is the placebo condition); 2) Cocaine (100 mg intranasally; a higher dose than tested in the study in our laboratory) plus hydromorphone (0 mg, intramuscular); 3) Cocaine (4 mg intranasally) plus hydromorphone (24 mg, intramuscular); and 4) Cocaine (100 mg intranasally) plus hydromorphone (24 mg, intramuscular). 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.

We know of only one human laboratory study that has determined the impact of d-amphetamine treatment on amphetamine self-administration [117]. In that study, subjects first sampled doses of oral d-amphetamine (0, 8 and 16 mg) and were then allowed to self-administer those doses on a progressive-ratio schedule following pretreatment with 0 and 15 mg of oral d-amphetamine. The sampled oral d-amphetamine dose maintained responding on the progressive-ratio schedule, but acute d-amphetamine pretreatment failed to alter self-administration.

Clinical Trials—The results of the initial clinical trials suggested that amphetamine isomers are effective for treating cocaine dependence [30, 118, 119]. In the seminal trial, for example, cocaine dependent patients were randomly assigned to receive d-amphetamine (15 or 30 mg/day; n=26 and 28, respectively) or placebo (n=40) for 25 weeks [118]. 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 using comparable d-amphetamine doses [30, 119].

In a more recent trial, cocaine dependent patients were randomly assigned to receive immediate-release methamphetamine (5 mg, 6 times/day; n=30) or sustained-release methamphetamine (30 mg in the morning and placebo 5 times/day; n=25) or placebo (6 times/day, n=27) for eight weeks [40]. Oral 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 percent in patients assigned to oral sustained-released methamphetamine, oral immediate-release methamphetamine and placebo, respectively, during the final week of the trial. This reduction in cocaine use is comparable to that observed with the most effective behavioral treatment for cocaine dependence, contingency management [20] and far exceeds what has been observed with other pharmacotherapies. Not surprising, 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 versus 30 mg). This “proof-of-concept” trial with a potent amphetamine isomer provides strong evidence for the continued development of agonist-like medications for managing cocaine dependence.

Three initial open label trials demonstrated that d-amphetamine maintenance reduces amphetamine use [120, 121, 122]. However, the two extant double-blind, placebo-controlled, randomized trials did not yield the same outcome [123, 124]. In the earlier double-blind study, the d-amphetamine treated group (110 mg sustained release/day [nearly twice the dose that showed efficacy in the cocaine clinical trials]; n=23) showed similar reductions in methamphetamine use, based on hair analysis, to what was observed in those receiving placebo (n=27) [123]. In the more recent study, 60 methamphetamine-dependent subjects were randomized to receive placebo (n=30) or 60 mg sustained release d-amphetamine/day (a dose shown to reduce cocaine use; n=30) for eight weeks [124]. Although d-amphetamine maintenance reduced methamphetamine craving, it did not significantly reduce the number amphetamine-positive urine samples.

Summary—The pharmacological and behavioral effects of amphetamines and cocaine overlap extensively, suggesting amphetamine isomers might function as an agonist replacement therapy for cocaine or amphetamine dependence. The literature reviewed here clearly supports the continued development of amphetamine isomers for cocaine dependence. Conversely, even though the pharmacological and behavioral effects of amphetamine isomers are very similar, d-amphetamine did not alter amphetamine self-administration, nor did it significantly reduce methamphetamine use in double-blind clinical trials, suggesting that d-amphetamine, or other dopamine releasers, may not be the ideal agonist replacement candidate for amphetamine use disorders.

Alternative Agonist Replacement Therapies for Stimulant Dependence: Modafinil

The literature reviewed above supports the utility of dopamine reuptake inhibitors and releasers as agonist replacement treatments for managing amphetamine and cocaine dependence, respectively. However, methylphenidate and d-amphetamine have significant abuse and diversion potential [e.g., 46, 93] and the efficacy of bupropion is limited to when it is combined with powerful behavioral treatments or tested in subsets of treatment populations. The viability of the agonist replacement approach for stimulant dependence may thus hinge on identifying novel agonist therapies that have less abuse and diversion potential and increased efficacy when administered alone or to broader populations. Considerable efforts have been directed towards identifying putative agonist replacement therapies that fit these criteria. Here, we review the data for modafinil because there is human laboratory self-administration and clinical trial research that has assessed the efficacy of this drug for cocaine and amphetamine dependence. There are other potential alternative agonist replacement therapies available like l-dopa/carbidopa or stimulant prodrugs, however, the clinical data regarding the efficacy of these compounds for cocaine and amphetamine dependence is relatively limited [for reviews, 47, 50].

Modafinil (Provigil®) is a novel stimulant indicated in the treatment of narcolepsy or excessive daytime sleepiness and may also be efficacious in managing ADHD [e.g., 125, 126, 127, 128, 129]. Doses of up to 400 mg modafinil/day (mean dose of 206 mg/day) are effective in managing ADHD [reviewed in 126]. 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 [130, 131, 132, 133]. One study, for example, used positron emission tomography to demonstrate that modafinil blocks dopamine transporters and increases extracellular

dopamine levels in humans [132]. It is important to note that modafinil also produces its effects through interactions with hypocretin/orexin, glutamate, GABA and noradrenergic systems [134].

Consistent with these biochemical data, the behavioral effects of modafinil overlap to some extent with those of prototypical stimulants [e.g., 135, 136, 137, 138]. In one study, the discriminative-stimulus effects of a range of doses of modafinil (3.2-32 mg/kg) were determined in rhesus monkeys (N=7) trained to discriminate 0.18 or 0.4 mg/kg cocaine [137]. Modafinil substituted for cocaine in six of seven monkeys. In a previous drug-discrimination study conducted in our laboratory, a range of doses of oral cocaine (50, 100 and 150 mg), modafinil (200, 400 and 600 mg) and placebo were tested in six participants with recent histories of cocaine use that had learned to discriminate 150 mg cocaine [139]. The two highest doses of modafinil partially substituted (i.e., approximately 46 and 54% drug-appropriate responding, respectively) for cocaine.

Whereas modafinil shares some pharmacological and behavioral effects with prototypical stimulants, it appears to have less abuse potential [140, 141, 142, 143]. 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) [144, cf. 136]. In a previous study in our laboratory, modafinil (0-600 mg) was nearly devoid of positive subjective effects [138]. A recent human laboratory study showed that modafinil (200-600 mg) did not function as a reinforcer using a choice procedure [145]. Overall, the neuropharmacological and behavioral effects of modafinil overlap to some extent with those of prototypical stimulants. Importantly, modafinil appears to have minimal abuse potential. These characteristics have prompted considerable interest in testing modafinil as a putative agonist replacement therapy for stimulant dependence.

Human Laboratory Self-Administration Studies

The results of human laboratory studies suggest modafinil attenuates the reinforcing effects of cocaine, but not methamphetamine [146, 147]. In the earlier 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) [147]. 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. In the more recent study, the reinforcing effects of intravenous methamphetamine (0 and 30 mg) were assessed in participants (n=13) maintained on modafinil (0 and 200 mg/day) [146]. Participants first sampled the available methamphetamine dose and then made 10 choices between 1/10th of that dose and saline. As expected, methamphetamine maintained responding, but modafinil failed to significantly reduce methamphetamine choice, although this lack of effect could be due to modafinil dose (i.e., 200 mg/day was the highest dose tested).

Clinical Trials

Three double-blind, placebo-controlled, randomized clinical trials have investigated modafinil for managing cocaine dependence and one trial investigated modafinil for methamphetamine dependence using doses similar to those tested in human laboratory studies [148, 149, 150, 151]. In the earliest trial, cocaine-dependent patients were randomly assigned to receive 400-mg/day modafinil (n=30) or placebo (n=32) for eight weeks. The modafinil-treated patients provided significantly more benzoylcegonine-free urines than the placebo-treated patients. A 12-week multi-site trial compared placebo (n=72) and modafinil (200 [n=69] and 400 mg [n=68]) [148]. 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. In the third trial for cocaine dependence, 210 patients were randomized to placebo (n=75), 200 mg modafinil/day (n=65) or 400 mg modafinil/day (n=70) combined with cognitive behavioral therapy for eight weeks [150]. Although modafinil did not reduce cocaine use in the overall sample relative to placebo, post-hoc analyses revealed that men receiving 400 mg modafinil/day tended to have greater levels of cocaine abstinence than those maintained on placebo. The apparent discrepancy between human laboratory and clinical trial data for managing cocaine use disorders may actually be reflective of modafinil's efficacy in sub-populations (i.e., individuals without co-morbid alcohol dependence and men were more likely to have reduced cocaine use during modafinil treatment; [130, 150]), which closely match the set of individuals enrolled in the human laboratory study (i.e., that study enrolled a predominantly male sample that was not alcohol dependent; [147]).

The clinical trial that tested modafinil for methamphetamine dependence randomly assigned patients to placebo (n=42) or 200 mg modafinil/day (n=38) for 10 weeks [151]. Modafinil failed to reduce methamphetamine use relative to placebo in the overall sample, but trends for improvement were shown in subsets of the population (i.e., those that were compliant, those without other substance dependence diagnoses and those that attended counseling sessions). As with the human laboratory study with modafinil and methamphetamine, this lack of effect could be due to only testing 200 mg/modafinil/day.

Taken together, these results suggest that modafinil may have modest efficacy for managing stimulant dependence in select populations. In light of the human laboratory and clinical trial data, modafinil may be more effective for cocaine dependence than for methamphetamine dependence.

Conclusion

Stimulant use disorders are an unrelenting public-health concern. A widely effective pharmacotherapeutic adjunct has yet to be identified and approved for managing stimulant use disorders. The clinical literature reviewed above suggests that agonist replacement therapy may be a viable option for managing stimulant use disorders, however. In this section we consider 1) which types of agonist replacement may be most effective for specific stimulant (i.e., cocaine or amphetamine) use disorders, 2) the concordance between human laboratory self-administration studies and clinical findings, as well as what information such human laboratory studies contribute to medications development efforts, 3) the place for and proper use of agonist replacement therapy for managing stimulant use disorders and 4) future directions.

Types of Agonist Replacement for Specific Stimulant Use Disorders

The gold standard clinical trial data reviewed above provide evidence that the pharmacological mechanism of action for a putative agonist replacement therapy impacts treatment outcome differentially based on the target stimulant of abuse. That is: dopamine reuptake inhibitors are more effective than dopamine releasers for reducing use of dopamine releasers (i.e., amphetamines) whereas dopamine releasers are more effective than dopamine reuptake inhibitors for reducing use of dopamine reuptake inhibitors (i.e., cocaine). Specifically, methylphenidate significantly reduced percentage of amphetamine-, but not cocaine-, positive urine samples during treatment in double-blind, placebo-controlled trials [e.g., 37, 77] whereas amphetamine isomers significantly reduced percentage of cocaine-, but not amphetamine-, positive urine samples in double-blind, placebo-controlled trials [e.g., 40, 118, 123, 124]. The finding that bupropion, a weak dopamine reuptake inhibitor, was

only effective when combined with a powerful behavioral treatment for cocaine dependence [98] had efficacy in sub-populations of amphetamine users without needing to be combined with contingency management and at doses that were generally ineffective for reducing cocaine use (i.e., 300 mg/daily) [24, 101] also is consistent with this notion. Given the similar pharmacological end target for cocaine and amphetamines (i.e., increased synaptic dopamine levels) and similar behavioral pharmacology of the drugs, development of medications for managing stimulant use disorders has often tested the same medications for both cocaine and amphetamines. The extant data reviewed here would suggest that pharmacotherapy development, particularly for agonist replacement therapy, instead needs to be tailored to the preferred drug of abuse for each patient. Thus, future research for cocaine dependence should focus on dopamine/monoamine releasers whereas future research for amphetamine dependence should focus on dopamine/monoamine reuptake inhibitors.

Concordance Between Human Laboratory and Clinical Trial Results

Overall, the outcomes of the available human laboratory self-administration studies are concordant with those of clinical trials, which supports the conclusions of previous reviews [53, 54]. Amphetamine analogs reduced cocaine self-administration in the human laboratory studies [72, 116] and also increased objectively verified cocaine abstinence [40, 118]. Moreover, bupropion pretreatment attenuated cocaine choice in a drug versus alternative reinforcer choice procedure, consistent with the demonstrated efficacy of bupropion when combined with contingency management [94, 98]. There are several instances in which it would appear that the human laboratory results contradict clinical trial findings, as described above. However, a closer look at these discrepant results could yield an alternate conclusion (i.e., that the outcomes point to details critical to demonstrating the efficacy of a putative agonist replacement). Thus, human laboratory studies may provide very specific information about the conditions in which agonist replacement medications might be effective, including target populations and dose.

It is important to note that human laboratory self-administration studies generally observe only modest reductions in drug taking produced by putative pharmacotherapies. The clinical relevance of such small reductions is unknown, but the outcomes clearly translate to clinical trial findings of enhanced drug abstinence. Research with cigarette smokers suggests that any reductions observed in non-treatment seekers, the population enrolled in human laboratory studies of stimulant self-administration, are magnified in individuals likely to seek treatment [152], so it is probable that a similar effect is occurring in stimulant abusing or dependent patients. Another important consideration is that complementary data are not available for methamphetamine to determine the positive predictive validity of human self-administration studies (i.e., there are no published human laboratory studies that have evaluated the effects of methylphenidate or bupropion treatment on self-administration of methamphetamine), but there appears to be negative predictive validity with amphetamines in that d-amphetamine and modafinil did not reduce self-administration or use [117, 123, 124, 146, 151].

Place for and Proper use of Agonist Replacement Therapies

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 stimulant dependence. Extended-release formulations of agonist replacements (e.g., Concerta® or Dexedrine Spansule®) are available and should be considered until effective alternatives are identified, particularly because extended-release preparations are less likely to be misused [153, 154, 155].

This review is intended to promote research and development of effective, acceptable agonist replacement-type medications for stimulant use disorders. The robust efficacy of some agonist replacement therapies (e.g., methamphetamine for cocaine dependence) clearly indicates that stimulant-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 stimulant dependence. From a clinical perspective, an effective agonist replacement therapy (e.g., methamphetamine or d-amphetamine) 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”, “rosetta stone” 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 also might identify the optimal conditions under which an agonist replacement therapy might be effective (e.g., target population, dose or providing non-drug alternative reinforcers). The use of agonist replacement therapy as a tool will eventually result in identifying an effective pharmacotherapy for stimulant dependence that is acceptable to clinicians.

Future Directions

Before closing, it is important to acknowledge an issue that is germane to the research reviewed here, but also to all medications development efforts for substance use disorders. That is, whereas the clinical trials reviewed above focused on the outcome of drug abstinence (i.e., percentage of drug-negative or positive urines as a function of treatment condition), whether complete drug abstinence “sets the bar too high” is currently under debate [156]. Complete abstinence is a common goal for 12-step type programs, but a different outcome like reduced drug use (i.e., what is commonly observed in human laboratory self-administration studies) may be a better achievable and thus more clinically relevant endpoint. Using such an outcome would allow for more successes to be observed in clinical studies and would eventually present more treatment options to those suffering from addiction. Adoption of different endpoints to define success of medications has been proposed in the treatment of other health problems [e.g., 157, 158], so such a change for substance abuse research would not be unprecedented. However, the onus is on researchers in the field of medications development for drug use disorders to define and empirically support an appropriate endpoint as we move forward in the approval process for putative addiction pharmacotherapies.

In addition to the future direction of examining other endpoints for demonstrating the success of substance use disorder pharmacotherapies, the outcomes reviewed above reveal several other important future directions: 1) more human laboratory self-administration research with putative agonist replacement pharmacotherapies with methamphetamine, 2) more research to examine the efficacy of alternative putative agonist replacement medications (e.g., stimulant prodrugs; l-dopa/carbidopa; drugs that act in monoamine systems but which have reduced abuse potential [e.g., atomoxetine]) and 3) determining the efficacy of putative agonist replacement medications combined with behavioral treatments because the use of medications alone will likely never be completely effective. Each of these directions will yield vital information and move the field closer to an FDA-approved agonist replacement treatment for stimulant use disorders.

Acknowledgments

Preparation of this manuscript was supported by grants from the National Institute on Drug Abuse (R01DA025032 [CRR], R01DA021155 [CRR], R01DA032254 [CRR], R21DA034095 [WWS]).

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