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Agonist-like pharmacotherapy for stimulant dependence: preclinical, human laboratory, and clinical studies

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A variety of natural and synthetic agents have long been used for stimulant properties, with nontherapeutic use producing multiple waves of stimulant abuse and dependence. The multitude of effects of stimulants exist on continua, and accordingly, here we characterize stimulant abuse/dependence and candidate pharmacotherapies in this manner. Behavioral therapy and medications have been investigated for treatment of stimulant abuse/dependence. Effectiveness of some behavioral interventions has been demonstrated. Most medications studied have been found to lack efficacy. However, an expanding literature supports use of agonist-like medications to treat stimulant abuse/dependence, a strategy effective for nicotine and opiate dependence. The agonist-like conceptualization for stimulant dependence posits that medications with properties similar to that of the abused drug, but possessing lesser abuse liability, will normalize neurochemistry and stabilize behavior, thus reducing drug use. Data suggest use of a range of medications, from L-dopa/carbidopa to amphetamine preparations, depending on the severity of use. This report reviews preclinical, human laboratory, and clinical trial data supporting the agonist-like approach, including risks and benefits. Future directions for development of agonist-like medications are also discussed.

Keywords: stimulant abuse; cocaine; methamphetamine; amphetamine; modafinil; bupropion; medication development; agonist; substitution; treatment

Introduction

History

A variety of botanicals have long been used for stimulant properties, including caffeine, coca (cocaine), khat (cathinone), and tobacco (nicotine). They have been used for a range of functions, from inducing euphoria, through relatively specific efforts to enhance performance, to pharmacotherapy for a range of disorders including attention deficit–hyperactivity disorder (ADHD), narcolepsy, and weight reduction. Amphetamine analogues and cocaine have had reasonable records as efficacious medications for several medical and psychiatric conditions, with early reports summarized in the first edition of the classic pharmacology text written by Goodman and Gilman.[1] There is little evidence that therapeutic regimens are problematic, and in fact narcoleptics generally take less than the prescribed stimulant regimens.[2] In contrast, abuse and dependence are more likely to emerge when stimulants are used for nontherapeutic purposes, especially when administered via injection, inhalation, or insufflation. This too has long been established, and Goodman and Gilman summarized the well-known potential risks and disastrous consequences of amphetamine analogues and cocaine.[1] During the last century, convergence of increased trafficking, diversification of preparations, and routes of administration resulted in successive waves of problematic use and social concern.[3–5] In recent decades, a period of increased nontherapeutic use of amphetamines occurred in the 1960s, another emerged in the 1990s and is ongoing, and cocaine abuse became prominent in the 1970s and has continued relatively unabated since.

Prevalence

World Health Organization prevalence data for 1998–2001 indicate that amphetamine-type stimulants, including MDMA, were used by approximately 40 million people worldwide, with an additional 13 million cocaine users. Abuse of amphetamine preparations has been particularly evident in East Asia and Oceania.[6] In the United States, the National Survey on Drug Use and Health (2007) estimates past year use of cocaine (all forms) at approximately 3% of the population 12 years and older and nonmedical use of stimulants (including methamphetamine) at slightly less than 2%.[7] In 2006 these drugs accounted for approximately 23% (14% cocaine and 9% stimulants) of all addiction treatment admissions in the United States.[8]

Risks of stimulant abuse and dependence

Medical consequences

Stimulant abuse, particularly frequent high-dose use, has multiple direct and indirect effects and can produce a plethora of adverse consequences.[9–15] Knuepfer's particularly thorough and well-integrated review (preclinical, human laboratory, and clinical) discusses cardiovascular pathology while noting the great individual variability in response and the absence of adequate data in some domains.[16] A systems review by Devlin and Henry points to the commonalities across the range of abused stimulants in terms of adverse events observed in emergency-room settings.[17] Still, it must be recalled that reports derived from emergency-room and medical examiner data often include multiple complicating factors contributing to reported events.[18]

Cognitive and psychiatric consequences

Aberrations in cognitive function and memory are widely reported to be associated with abuse of cocaine and amphetamines.[19,20] De Sola Llopis *et al.* graded cognitive deficits (noted to be "subclinical") in a clinical population of MDMA users as a function of total lifetime drug consumption,[21] and Bedi and Redman suggested absence of deficits except with high-dose use.[22] Prominent effects of MDMA use on cognitive function were reported by Schilt *et al.*, albeit with uncertainty about functional or long-term consequences.[23] Horner, in a detailed review of abstinent cocaine users, suggested absence of attention deficits or clear sequelae to use.[24] Still, structural and/or neurochemical change or damage as a consequence of prolonged high-dose stimulant abuse should be expected.

Psychiatric symptoms associated with high-dose stimulant abuse have been long and frequently reported.[25] Rounsaville has addressed the problem of depression, commonly associated with use and abstinence.[26] Jacobs and others[27–29] noted abundant similarities between schizophrenics and patients having methamphetamine-induced psychotic disorder. These and other reports published over many decades document the potential severe psychiatric consequences of stimulant abuse.

Continuum of symptom severity and pharmacotherapy requirements

The spectrum of appetitive, aversive, and adverse effects produced by stimulants has been described from varied perspectives. For example, Post provided a thorough review of stimulant effects in terms of models of psychopathology.[25] Symptoms were described in a continuum, ranging from modest, arguably positive, through seriously impairing, to catastrophic behavioral/psychological disruption (Table 1). He also addressed the linkage between severity, chronicity of administration, and dose.

One can similarly consider the characteristics of stimulant abuse and dependence as existing on a continuum. The patterns of use would generally predict severity of drug abuse and dependence as well as the severity of behavioral/psychiatric symptoms. A variety of agents might be used for treatment of abuse or withdrawal-related symptoms. However, with respect to decreasing (i.e., treating) drug seeking and drug taking, pharmacotherapeutic agents can be categorized for likely utility on the basis of the use patterns/amounts as surrogates for "severity." The continuum of drug use includes the following categories: low, intermediate, and high dosing, with each category further subdivided by intermittent versus chronic use. This directs attention to a rational pharmacotherapeutic strategy. Testable inferences can be stated concerning the necessity and utility of a continuum of candidate pharmacological agents, here considered in terms of agonist-like agents, for treatment of stimulant abuse and dependence. At present, this is supported by data ranging

Table 1. Continuum of symptom severity

Cocaine euphoria	Cocaine dysphoria	Cocaine schizophreniform psychosis
Euphoria	Sadness	Anhedonia
Affective lability	Melancholia	Lack of disorientation
Intellectual function increase	Apathy	Hallucinations
Hyperalertness	Inability to concentrate	Concern with minutiae
Hyperactivity	Painful delusions	Stereotypic behavior
Anorexia	Anorexia	Paranoid delusions (parasitosis)
Insomnia	Insomnia	Insomnia
Hypersexuality		Prone to violence
Prone to violence		

Modified after Post, 1975, Appendix A.[25] The behavioral/psychiatric symptoms associated with stimulant abuse and dependence overlap and differ in severity as a function of individual characteristics, amounts of drug, and patterns of use. The symptoms point to a general frame for delineating requirements for medications.

from L-dopa/carbidopa, through modafinil, to amphetamine analogues.

Behavioral and pharmacological treatments for stimulant dependence

Extensive efforts have been directed at developing behavioral and pharmacological treatment strategies for stimulant abuse and dependence. Of these strategies, behavioral therapy has demonstrated some success.[30] The strategies and coping skills taught in cognitive behavioral therapy (CBT) have consistently been shown to reduce cocaine use in dependent individuals, with some sustained benefit after treatment.[31,32] Similarly, the Matrix model, which includes CBT components, reduced methamphetamine use.[33] Contingency management, a strategy that provides money, vouchers, or other reinforcers contingent on negative drug screens, also reduces cocaine or methamphetamine use.[30,34,35]

It can be expected that combinations of behavioral therapy and medications might be optimal. Researchers have spent several decades investigating medications to treat stimulant abuse and dependence and yet no universally effective pharmacotherapy has been identified or approved for this indication. Medications investigated include antidepressants, anticonvulsants, and antipsychotic agents, with mostly equivocal results.[36] However, a promising strategy uses the replacement, or agonist-like, approach. Agonist, or substitution, therapy is used to treat disorders, such as diabetes, as well as substance use disorders, such as opiate and nicotine dependence. The agonist-like conceptualization for stimulant dependence posits that administration of a long-acting stimulant should stabilize neurochemical and behavioral perturbations. Inherent to this approach is the use of a well-defined, carefully monitored dosing regimen. This review considers (1) preclinical underpinnings and data, (2) human laboratory data, and (3) clinical trial data, followed by a summary of benefits and risks along with future directions for examining utility of medications in the context of the agonist-like framework.

The agonist case summarized

In the realm of specific drug actions, rather than symptomatic treatment, two approaches have been used to pursue pharmacotherapeutic agents for stimulant dependence. One focuses on identifying a "stimulant antagonist." The premise is that treating patients with an antagonist will block the desired effects of cocaine or methamphetamine (e.g., euphoria), thereby leading to the extinction of the behaviors of drug taking and drug seeking. Antagonist therapies, such as mecamylamine and naltrexone, can be effective for nicotine and opioid dependence, respectively, with carefully established regimens.[37–39] Preclinical and human laboratory studies have identified several compounds that attenuate the behavioral effects of cocaine, but none of these drugs has proven effective clinically.[40–43] 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.[44–46]

An alternative to the antagonist approach is agonist-like replacement therapy. By definition, an agonist-like medication should possess neurochemical and behavioral effects similar to those of the abused drug, with minimal abuse liability. The dopamine (DA), serotonin (5-HT), and norepinephrine (NE) systems are valid targets for agonist-like medications because of their prominent role in the neurochemical effects of cocaine and amphetamines,[47–51] although there is no consensus for targeting single versus multiple transmitter systems.[36,52]

The DA system is an important target because of its role in psychostimulant reinforcement and deficits in DA function resulting from chronic stimulant abuse[53–57]; however, although DA enhancement may be necessary, it may not be sufficient to treat stimulant dependence.[36,52] Importance for the DA system is supported by preclinical and clinical studies with D-amphetamine (see the following text), although it also has effects on other transmitter systems. The utility of agonist-like medications with action to enhance 5-HT or NE systems is less clear. These systems do contribute to the effects of psychostimulants,[50,58–60] although clinical studies with selective 5-HT[61,62] or NE[63,64] medications have produced mixed results in the absence of concurrent dopaminergic action. Interestingly, accumulating evidence supports benefit from agonist-like medications that broadly enhance monoamine transmission (see Ref. 65 for review and Future directions).

Preclinical studies

Preclinical models are important in the drug development process because they provide a high-throughput means to test potential medications, including those not approved for administration to humans. Significant findings can then be tested in translational human laboratory studies. Just as important, preclinical studies permit rigorous control of genetic, environmental, and pharmacological factors that might otherwise obscure findings. Many preclinical models have been developed to characterize the neurochemical and behavioral effects of abused drugs. The appetitive effects of psychostimulants are associated with enhanced levels of DA in the nucleus accumbens,[53] an effect that can be measured with microdialysis. Also, several behavioral assays are used in animal studies, two of which will be discussed. The first assay, the drug discrimination paradigm, provides a preclinical model of subjective effects of drugs in humans,[66] whereas the second procedure, self-administration, directly evaluates drug taking. The use of self-administration procedures is predicated on the notion that reinforcing effects of stimulants are central to their abuse.[67] Medications replacing some actions and attenuating reinforcing efficacy of the illicit agent would be predicted to be effective clinically because biological, behavioral, and environmental determinants of drug taking would have diminished strength.[68–70]

Several promising agonist-like medications that enhance dopaminergic function have been investigated in preclinical studies, including D-amphetamine, methylphenidate, modafinil, and bupropion. Because an agonist-like medication should share effects with the abused drug, we first describe neurochemical (microdialysis) and behavioral (drug discrimination, self-administration) commonalities across some abused agents and candidate medications. Efficacy of putative agonists in reducing psychostimulant self-administration or drug discrimination is then considered.

D-Amphetamine

D-Amphetamine is a medication used clinically for the treatment of ADHD and narcolepsy.[71] It acts as a substrate at monoamine transporters to increase transmitter release through a carrier-mediated exchange system and action at presynaptic vesicles,[72] resulting in increased extracellular levels of DA and NE.[48,73] Preclinical studies support D-amphetamine as an agonist-like medication on the basis of the similarities between the neurochemical and behavioral effects of D-amphetamine and cocaine or methamphetamine. For example, microdialysis studies indicate that D-amphetamine,[74] like cocaine[49] and methamphetamine,[74] enhances extracellular DA in the nucleus accumbens, a brain region implicated in drug reward. Also, D-amphetamine substitutes for cocaine[75] or methamphetamine[76] in the drug discrimination paradigm, suggesting that these compounds generate a similar interoceptive

cue. Furthermore, D-amphetamine, like cocaine or methamphetamine, is an effective reinforcer in animal self-administration studies.[77]

Several preclinical studies have examined the ability of D-amphetamine to attenuate cocaine self-administration. In one, rhesus monkeys were trained to self-administer cocaine and food, with each reinforcer available during independent daily sessions.[78] Following acquisition of self-administration, animals were chronically treated with D-amphetamine for 28 days via intravenous (i.v.) catheter; food and cocaine reinforcement were measured each day during this period. Compared to basal levels of reinforcement, both cocaine and food self-administration were suppressed during the first few days of D-amphetamine treatment. Predictably, food self-administration returned to baseline levels by approximately the ninth day, reflecting tolerance, whereas cocaine self-administration was virtually eliminated for the duration of the 28-day study. In the week after cessation of D-amphetamine treatment, cocaine self-administration returned to baseline levels. These results and others by Negus, Mello, *et al.* clearly indicate that chronic D-amphetamine treatment produces a sustained, selective reduction in cocaine reinforcement.

Attenuation of cocaine reinforcement with chronic D-amphetamine treatment has also been reported in rats,[79] and D-amphetamine reduced cocaine reinforcement in a cocaine–food choice procedure.[80] In a subsequent study, Mello and Negus[81] found that chronic administration of D-amphetamine plus the opiate agonist buprenorphine selectively reduced self-administration of speedball, a combination of cocaine and heroin. Collectively, these data suggest potential for D-amphetamine to reduce cocaine use in humans. Further, combinations of stimulant and opiate agonist-like medications may be useful to concurrently treat dual cocaine and heroin dependence, a premise also supported by clinical studies (see Clinical trials).

Another evaluative strategy examines the effects of acute pretreatment with a potential agonist replacement therapy on the discriminative effects of a drug of abuse. As noted in the preceding, drug discrimination in animals is thought to be a model of subjective effects in humans. In a recent study, DA releasers and uptake inhibitors were evaluated to determine whether they altered the discriminative-stimulus effects of cocaine in rats.[75] Acute pretreatment with either DA releasers or uptake inhibitors shifted the cocaine dose–response curve leftward; that is, it produced additive or even supra-additive effects. The DA releasers, specifically D-amphetamine and methamphetamine, were more potent in shifting the curve leftward than the DA uptake inhibitors, such as methylphenidate and GBR 12909.[75] Czoty *et al.* also found this leftward curve shift in the discriminative-stimulus effects of methamphetamine when pretreating with the DA uptake inhibitors GBR 12909 and AM2517, although they did not make direct comparisons with DA releasers.[82] Collectively, these data suggest DA releasers, such as D-amphetamine that elicit the greatest shift in the stimulant dose–response curve, have substantial and perhaps greater promise compared to DA reuptake inhibitors.

Methylphenidate

Methylphenidate is a stimulant medication that, like D-amphetamine, results in increased extracellular monoamine levels; however, methylphenidate does so via a distinct mechanism. Methylphenidate binds to monoamine transporters and inhibits reuptake, with the greatest selectivity for the DA transporter rather than the 5-HT or NE transporter.[83] Like D-amphetamine, methylphenidate is approved by the U.S. Food and Drug Administration (FDA) for the treatment of ADHD,[71] and some preclinical studies support its use as an agonist-like medication. Microdialysis studies demonstrate that methylphenidate enhances DA levels in the nucleus accumbens.[83] Drug discrimination data indicate that methylphenidate substitutes for cocaine[75] or methamphetamine,[84] and methylphenidate sustains self-administration in animal studies.[85] A recent study documented the ability of chronic methylphenidate to reduce cocaine reinforcement in rodents. Specifically, 8 months of oral methylphenidate administration, beginning in adolescence, resulted in a subsequent decrease in cocaine self-administration.[86] Further support for methylphenidate as an agonist-like medication was provided in the drug discrimination study described in the foregoing (see D-amphetamine section) by Li *et al.*[75] In sum, these preclinical studies support methylphenidate as a potential agonist-like medication.

Modafinil

Modafinil is a novel stimulant-like agent administered for treatment of narcolepsy and to attenuate fatigue/sleepiness associated with shift work.[87,88] The mechanism of action of modafinil is not completely understood, with proposed action at DA, NE, and glutamate systems.[89–92] Consistent with its ability to weakly inhibit DA reuptake, the behavioral effects of modafinil overlap to some extent with those of prototypical stimulants, including enhanced extracellular DA in the nucleus accumbens.[90,92] Modafinil partially substitutes for the discriminative stimulus effects of cocaine and is self-administered, although only at high doses[93,94]; these data suggest some similarity between modafinil and classical psychostimulants. However, modafinil does not block cocaine self-administration in animals[93] (but see Human laboratory studies). Together, these data indicate that modafinil possesses subtle stimulant-like effects, and several clinical studies support its use as an agonist-like medication.

Bupropion

Bupropion is an effective antidepressant and is used as an adjunct in smoking cessation.[95,96] The behavioral effects of bupropion overlap to some extent with those of prototypical stimulants, which is consistent with its action at the DA transporter and enhancement of extracellular DA levels in the nucleus accumbens.[92,97] Also, bupropion substitutes for cocaine[98] or methamphetamine[99] in drug discrimination studies and is self-administered by laboratory animals.[85] Reichel *et al.* recently investigated the ability of several bupropion doses to block maintenance of methamphetamine or sucrose self-administration. They reported that bupropion treatment reduced methamphetamine reinforcement, with some specificity compared to sucrose reinforcement.[100]

Human laboratory studies

Human laboratory experiments designed to determine the efficacy of a putative pharmacotherapy typically administer a range of doses of an abused stimulant (e.g., cocaine or methamphetamine) while volunteers are maintained on various doses, including placebo, of the candidate medication. The behavioral outcome measures used to assess the effects of abused stimulants in humans sometimes include sophisticated drug self-administration procedures that characterize reinforcing efficacy and thus abuse potential.[67]

More often, however, the primary outcome measures are self-reported "subjective-effects" questionnaires. Some of the questionnaires are standardized (e.g., Addiction Research Center Inventory [ARCI] or Profile of Mood Stats), whereas others are investigator developed (e.g., Drug Effect Questionnaire). The premise of these studies is that the positive subjective effects of stimulants contribute significantly to their abuse. Medications attenuating subjective effects of the abused stimulant would be predicted to be effective clinically because drug taking would diminish or cease because the drug-dependent patient no longer experiences the desired effects. However, the linkage between self-report (verbal behavior) and probability of drug taking can diverge substantially.

Regardless of the outcome measure, human laboratory experiments are an integral component of the medication development process for at least three reasons. First, human laboratory experiments can be conducted rapidly and efficiently. Although double-blind, placebo-controlled, randomized trials are the "gold standard" of clinical research, they are costly, time consuming, and labor intensive. These trials should be conducted with only the most promising medications for the management of stimulant dependence. Human laboratory studies are needed to further vet candidate medications that have been demonstrated to be effective in preclinical laboratory paradigms. Second, human laboratory studies might identify the optimal conditions (e.g., dose) under which a putative pharmacotherapy might be expected to be effective and well tolerated. Third, the conduct of human laboratory studies provides important bidirectional translational information. As described previously, agonist replacement therapies for stimulant dependence have been tested in laboratory animals by using drug self-administration and discrimination procedures.[78–81] The conduct of similar studies in humans partly determines the predictive validity of models used in preclinical experiments. Moreover, the positive clinical findings with agonist-like replacement therapies can now be used as a reference to determine the predictive validity of human laboratory procedures used to screen putative pharmacotherapies for stimulant dependence. Identifying an effective pharmacotherapy for

stimulant dependence has been limited, in part, by uncertainty regarding the predictive validity of the laboratory methods used to screen novel medications. A "bedside-to-bench" or "reverse engineering" strategy allows investigators to refine the human laboratory methods used to determine the efficacy of putative pharmacotherapies for stimulant dependence.

Next we review human laboratory studies assessing agonist replacement pharmacotherapies for the management of stimulant abuse with self-administration, drug discrimination, and subjective-effects questionnaires. The results of these studies are typically, though not always, concordant with those of preclinical experiments and suggest agonist-like replacement therapy to be a viable strategy for managing stimulant dependence.

D-Amphetamine and methylphenidate: human drug self-administration

Two human laboratory studies have examined the ability of an agonist-like replacement therapy to attenuate the reinforcing effects of cocaine in cocaine-dependent participants (Rush *et al.*, manuscript under review).[101] In the first, reinforcing effects of i.v. cocaine (0, 16, and 48 mg) were assessed in those with ADHD/cocaine dependence ($n = 7$) maintained on methylphenidate (0, 40, and 60 mg/day).[101] Using the self-administration paradigm, participants sampled a dose of cocaine (16 or 48 mg, i.v.) and were then given five opportunities to choose between it and a $2.00 token. Participants chose the 48-mg i.v. cocaine dose four of five times during placebo maintenance. Methylphenidate maintenance (e.g., 60 mg/day) significantly reduced choice of the 48 mg i.v. cocaine dose (e.g., two of five choices).

In the second study, nine cocaine-dependent participants were maintained on placebo or D-amphetamine (40 mg/day) in counterbalanced order (Rush *et al.*, manuscript under review). After 3–5 days of amphetamine maintenance, volunteers completed five experimental sessions. During these sessions, the participant first sampled placebo (e.g., here, an ineffective dose of 4 mg of intranasal cocaine) identified as Drug A and then sampled a second intranasal drug dose (4, 10, 20, or 30 mg of cocaine) identified as Drug B. Volunteers subsequently made six discrete choices (separated by 45 min) between Drug A and Drug B. The primary outcome measure was choice differential (i.e., drug choices minus placebo choices). All doses of cocaine alone increased the choice differential score significantly above levels observed with placebo during the control maintenance period, whereas only the low and high doses of cocaine did so during D-amphetamine maintenance. The choice differential score was significantly lower for 20 mg of cocaine during D-amphetamine than for placebo maintenance. Overall, the results indicate that D-amphetamine attenuates reinforcing effects of cocaine.

The agonist-like therapies tested in these self-administration studies did not completely suppress drug taking, as was observed in the preclinical experiments described in the preceding. The reasons for the discrepancy between preclinical and human laboratory experiments may be attributable to differences in experimental parameters, confounds, and the drug history of human subjects. For example, the preclinical studies tested higher doses of agonist medications, with animals maintained on the medication for a considerably longer duration. A further problem in translation and prediction of efficacy in the clinic is that there are upper limits on dosing with the abused drug in laboratory studies with volunteers; these may not adequately approximate patterns of drug use in naturalistic settings. Notwithstanding such limitations, the human laboratory studies provide invaluable data. Still, future human laboratory studies should examine higher doses of D-amphetamine (40–60 mg/day) or methylphenidate (e.g., 80–120 mg/day) in participants that have been maintained on medication for a longer period, and where feasible, challenges with higher doses of the abused drug would be informative.

D-Amphetamine and methylphenidate: human drug discrimination

As reviewed in the preceding (see Preclinical studies), acute doses of promising agonist replacement therapies should be expected to shift the dose–response curve of the training drug leftward when animals are trained to discriminate cocaine or methamphetamine.[75,82] That is, the profile should parallel that of the abused agent. Johanson *et al.* examined this question by comparing two routes of cocaine administration rather than two different drugs.[102] Participants ($n = 8$) learned to discriminate between i.v. cocaine (20 mg/70 kg of

body weight) and saline. After the discrimination was acquired, a range of doses of i.v. cocaine (5–40 mg/70 kg) were tested alone and after pretreatment with oral cocaine (0 and 300 mg/70 kg). Acute pretreatment with oral cocaine enhanced the subjective and cardiovascular effects of i.v. cocaine and shifted the i.v. cocaine dose–response curve up and to the left. Not surprisingly, oral cocaine is perceived as having similarities, though is not identical, to i.v. cocaine in this study.

In a similar study in which the training drug and agonist medication were administered by the same route, here orally, participants ($n = 5$) learned to discriminate between oral methamphetamine (10 mg) and placebo (Vansickel *et al.*, unpublished data). After acquiring the discrimination, a range of doses of oral methamphetamine (2.5–10 mg) was tested alone and after pretreatment with oral D-amphetamine (0 and 15 mg). D-Amphetamine robustly shifted the methamphetamine dose–response curve up and to the left. These findings are consistent with the notion that when given acutely, candidate agonist replacement therapies should be expected to shift the cocaine or methamphetamine dose–response curve leftward in the drug discrimination paradigm. Although seemingly counterintuitive, the leftward shift with acute administration indicates that the medication has elements of an agonist profile that will enhance its efficacy in a therapeutic regimen. This parallels the finding that agents demonstrably effective as agonists in replacement regimens (e.g., D-amphetamine) can produce priming or reinstatement when administered acutely in the self-administration paradigm.

D-Amphetamine and methylphenidate: self-report, subjective-effects questionnaires

Four human laboratory studies considered here assessed the subjective effects of cocaine in participants maintained on an agonist replacement therapy.[101,103–105] In the seminal study, the subjective effects of i.v. cocaine (0, 25, and 50 mg) were assessed in participants maintained on oral cocaine (0, 25, 50, and 100 mg, four times daily).[104] In the second experiment, cocaine-dependent participants were maintained on D-amphetamine (0, 15, and 30 mg/day) for 3–5 days.[103] In the other two studies, participants were maintained on 0-, 60-, and 90-mg/day[105] or 0-, 40-, and 60-mg/day methylphenidate.[101] During each maintenance phase, a dose–response function was determined for i.v. (0, 25, and 50 mg)[101,104,105] or intranasal[103] cocaine. Cocaine produced prototypic and predictable stimulant-like subject-rated effects (e.g., increased ratings of Good Effects, Drug Liking, Willing to Take Again) that were generally a function of dose. Maintenance on these agonist replacement therapies significantly attenuated some of the subjective effects of cocaine.

Modafinil

Human laboratory studies with the stimulant-like agent modafinil were also conducted. In a previous study conducted in our laboratory, six human volunteers with recent histories of cocaine use learned to discriminate 150 mg of oral cocaine.[106] After acquiring the discrimination (e.g., $\geq$80% correct responding on 4 consecutive days), a range of doses of oral cocaine (50, 100, and 150 mg), modafinil (200, 400, and 600 mg), and placebo were tested to determine whether they shared discriminative-stimulus effects with 150 mg of cocaine. The two highest doses of modafinil, 400 and 600 mg, partially substituted (i.e., approximately 46% and 54% drug-appropriate responding, respectively) for cocaine. Oral cocaine produced robust stimulant-like subjective effects (e.g., increased ratings of Good Effects and Drug Liking). Modafinil, by contrast, was nearly devoid of psychoactive effects as determined by these measures. These findings suggest that modafinil has minimal abuse potential and may be a viable agonist replacement therapy for stimulant dependence.

Consistent with this notion, the results of human laboratory experiments suggest that modafinil attenuates the reinforcing and subjective effects of cocaine.[107–109] In an elegant 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).[108] 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. Both doses of modafinil significantly decreased choices of the intermediate and high cocaine doses. In two laboratory experiments effects of i.v. cocaine (0–40 mg) were assessed in participants pretreated with modafinil (0, 200, and 400 mg/day for 4 days[107]; 0, 400, and 800 mg/day

for 7 days[109]). During placebo maintenance, i.v. cocaine produced prototypical subjective effects (e.g., increased scores on the amphetamine [A] scale of the ARCI). Modafinil dose-dependently attenuated the some of the subjective effects of cocaine.

Collectively, these laboratory findings with modafinil suggest promise because this medication attenuated cocaine self-administration. Human self-administration procedures appear to have considerable predictive validity for identifying medications that may be clinically effective for managing stimulant dependence.[69,70]

Bupropion

Human laboratory studies with bupropion further elucidate its effects and profile for utility in stimulant abuse treatment. In one study, a range of doses of bupropion (50–400 mg) was assessed in five participants that had learned to discriminate 20-mg oral D-amphetamine.[110] The two highest doses of bupropion, 200 and 400 mg, partially substituted (i.e., approximately 20–40% drug-appropriate responding) for D-amphetamine. D-Amphetamine and bupropion produced a similar constellation of stimulant-like subjective effects. Whereas these findings suggest bupropion may be a viable agonist replacement therapy for stimulant dependence, other data suggest limitations.

In one laboratory experiment, subjective effects of intranasal cocaine (0, 50, and 100 mg/70 kg) were determined in volunteers maintained on 150- and 300-mg/day bupropion ($n = 7$).[111] 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 Good Effects and Drug Liking). Bupropion maintenance did not alter the subjective effects of cocaine.

Two studies have assessed the subjective effects of methamphetamine in participants maintained on or pretreated with bupropion (Vansickel *et al.*, unpublished data).[112] In one, the subjective effects of i.v. methamphetamine (0, 15, and 30 mg) were determined in volunteers maintained on 300-mg/day bupropion ($n = 10$) or placebo ($n = 10$).[112] Both doses of methamphetamine increased subjective ratings of "any effect" and "high" in placebo- and bupropion-maintained volunteers. The magnitude of these effects was significantly less in the bupropion-maintained volunteers. Bupropion also attenuated cue-induced increases in subjective ratings of craving. In the second study, participants ($n = 5$) learned to discriminate between oral methamphetamine (10 mg) and placebo (Vansickel *et al.*, unpublished data). After the discrimination was acquired, the discriminative and subjective effects of a range of doses of oral methamphetamine (2.5–10 mg) were tested alone and after pretreatment with oral bupropion (0 and 150 mg). Bupropion did not significantly alter the discriminative effects of methamphetamine. Methamphetamine produced a constellation of positive subjective effects (e.g., increased ratings of Good Effects) that were an orderly function of dose. Bupropion pretreatment significantly attenuated these effects, as evidenced by a significant interaction of bupropion and methamphetamine.

Although the effect observed with bupropion and methamphetamine is intriguing, it must be viewed cautiously because subjective-effects questionnaires were used as the primary outcome measure. The predictive validity of these instruments is unclear.[69,70] Therefore, it is critical that future human laboratory studies determine whether bupropion attenuates self-administration of cocaine or methamphetamine.

Clinical trials

Encompassing reviews, for example, Cochrane reports, of candidate treatment medications for stimulant dependence are available and the summations are largely negative. Amato *et al.*[113] clearly indicated the absence of support for administration of antipsychotic medications, whereas Minozzi *et al.*[114] reported no significant benefit of anticonvulsant agents. The agonist-like treatment literature for stimulant abuse and dependence varies greatly in type and rigor. There are few rigorous controlled trials that have examined the plausible available agents. This diminishes utility of Cochrane or other meta-analytic reviews' strategies. Some review articles have, in the main, avoided consideration of robust multiaction medications for treatment of stimulant abuse and dependence. Still, three previous review articles emphasizing clinical trials have focused on use of agonists for treatment of stimulant dependence.[41,52,115] Other reviews, such as those by Rothman *et al.*,[65] have

focused on expanding the agonist conceptualization on the basis of robust stimulants. Thus, Rothman *et al.*[116] have argued for a logical extension to the potent agonist conceptualization, noting that ideal medications would have combined dopaminergic and serotonergic action. Here we summarize the clinical literature to date, ordered by relative robustness of agonist profile: methamphetamine, D-amphetamine, modafinil, methylphenidate, bupropion, and L-dopa/carbidopa.

Methamphetamine

A variety of agonist-like agents have been investigated to treat stimulant dependence. For example, Llosa found benefit for oral cocaine preparations to treat stimulant dependence.[117] Aside from Llosa's studies of cocaine, perhaps the agonist-like agent least likely to find clinical acceptance, in part because of an early study, is the mixed DA/5-HT/NE releaser methamphetamine. The first such study is thought to have substantially dimmed enthusiasm for pursuit of a broader agonist approach for several decades. Mitcheson *et al.* declared stimulant replacement a failed strategy after administering injectable methamphetamine to patients with relatively brief histories of stimulant abuse.[118] Because the premise of an optimally effective agonist-like approach is to diminish peaks and troughs, decrease rapidity of onset, and change problematic behaviors, the report of failure with i.v. methamphetamine is not surprising. It might be argued that Mitcheson *et al.* presaged a different strategy, that of the harm reduction approach of "injection rooms" for heroin dependence, but their strategy lacked crucial elements of agonist-like pharmacotherapy.

More concordant with a rational agonist-like approach, Mooney *et al.* recently reported distinctive efficacy of oral methamphetamine for treatment of cocaine dependence.[119] A second goal of the study was to examine the relative effectiveness of equivalent total doses of sustained release (SR; single dose) versus immediate release (IR; divided dose) preparations compared to placebo. Mooney *et al.* reported no differences in retention across the three groups (SR, IR, placebo) but that active medication was safe and well tolerated. Most interesting was the dramatic reduction in cocaine use from 30 mg/day of methamphetamine SR, with ~10% positive urine samples by the end of treatment; no benefit was found for the IR group. The difference between the two active groups despite equivalence of dose available (30 mg/day) was readily explained. All subjects were to have ingested six capsules/day. Compliance with the complete multicapsule regimen quickly faded, but the first dose of the day was usually ingested. The SR group was thus successfully administered 30 mg of methamphetamine. However, by ingesting the first one or two capsules of the day, the IR group received $\leq$10 mg/day of methamphetamine. Only one subject of the 55 receiving active medication was discharged because of "intolerance of study medication." This clinical trial with a robust amphetamine analog with mixed action at DA, 5-HT, and NE systems has provided the strongest positive result of all medications described in this review.[119] This proof-of-concept study provides strong evidence for further development of agonist-like medications with broad action to enhance DA/5-HT/NE systems (see Future directions and Ref. 65).

D-Amphetamine

Prior to, or concurrent with, rigorous double-blind randomized controlled trials, several reports described presumed therapeutic administration of D-amphetamine to stimulant-abusing patients, typically in community clinics. Other reports were case series or retrospective chart reviews after clinical administration of oral D-amphetamine. All used IR rather than SR preparations. Cumulatively, the results indicate benefit of D-amphetamine/agonist administration to hundreds of patients who were typically i.v. amphetamine abusers. These reports were generally from the United Kingdom or Australia and are of interest because they stem from clinical environments and diverse populations (for more thorough discussion, see Refs. 41, 52, and 115). Further, some included up to a year or more of maintenance on oral D-amphetamine.

Sherman examined refractory patients with extended histories of methamphetamine use treated with oral D-amphetamine (20–90 mg); most exhibited some benefit.[120] A sample of patients treated with oral D-amphetamine doses of 30 mg, deemed inadequate and subsequently increased up to 60 mg, were found to benefit and have no adverse consequences during maintenance.[121] Pates *et al.*, administering up to 60 mg of oral D-amphetamine, reported decreases in injection of illicit amphetamines; here one patient had an

adverse psychiatric event.[122] McBride *et al.* described reductions in use of i.v. amphetamines and excellent retention in patients receiving 40-mg oral D-amphetamine per day.[123] Notable was a study by Merrill and Tetlow, who more rigorously monitored use through specialized urine screen procedures differentiating amphetamine isomers. They reported both discontinuation and reduction of illicit amphetamine use in the more than 50% of patients who remained in treatment at 1 year.[124] In another study, enhanced retention and reduction in amphetamine abuse/dependence were also reported.[125] Merrill and Tetlow, using higher doses, reported significant response within 1 month,[124] whereas Grabowski *et al.*,[45,126] using a stepped procedure, reported the greatest benefit to occur at 2–3 months. These results, combined with the broader literature, argue for higher doses earlier in treatment.

A striking report was that from 1998 by Charnaud and Griffiths.[127] They examined effectiveness of oral D-amphetamine, again in i.v. amphetamine users. They compared the result to effectiveness of methadone for treatment of heroin dependence in their population. Sixty-seven percent of heroin users receiving methadone terminated drug use and 21% reduced use, whereas 70% of the i.v. amphetamine users receiving oral D-amphetamine terminated use and 27% reduced use. In a complete record review, White reported 50% cessation in i.v. amphetamine use in individuals receiving up to 90 mg of oral D-amphetamine.[128]

Several of the preceding reports described adverse psychiatric events, typically in individuals who continued injecting high doses of illicit stimulant or who had unreported histories of psychosis. In an unusual but interesting report, Carnwath *et al.* described patients with diagnosed major psychoses maintained on antipsychotics who also abused amphetamines.[129] Administration of oral D-amphetamine produced reduction in illicit amphetamine use, no interference with antipsychotics, enhanced compliance with antipsychotics, and no instances of exacerbation of psychiatric symptoms.

In 2001, Shearer *et al.* described the first randomized controlled trial of D-amphetamine for D-amphetamine abuse with supplementary behavior therapy in an extremely heterogeneous population attending a community clinic.[130] Patients received up to 60 mg of D-amphetamine IR once daily. Both groups showed evidence of improvement, with a trend for greater improvement in the medication group.

Two large placebo-controlled trials examined D-amphetamine SR for treatment of cocaine dependence.[45,126] These studies, initiated in the late 1990s, took a cautious dose-escalating approach. In the first study, cocaine-dependent subjects received 15 or 30 mg/day of D-amphetamine SR or placebo for an initial 4-week period.[126] The D-amphetamine dose was subsequently doubled to 30 or 60 mg/day, with medication administration for 8 additional weeks. Multiple urine screens were obtained weekly and electrocardiograms were obtained twice monthly. Benzoylecgonine-positive screens diminished in the high dose (30 escalating to 60 mg/day) group over the course of the trial. Notable was the secondary finding that the greatest effect appeared for subjects who entered the study with positive urine screens, arguably a surrogate for severity. Achieving benefit in the more severe population is important because the usual finding is that negative baseline urine screens alone predict success, whereas positive samples predict less successful outcomes.[131]

Shearer *et al.* conducted a controlled community trial with a heterogeneous population of cocaine users having complex collateral problems (e.g., sex workers and methadone patients) in which oral IR D-amphetamine was administered.[132] The group receiving D-amphetamine had improvement on several dimensions, including reductions in drug use compared with that of the control group. One instance of psychiatric problems emerged in a subject with an undisclosed history of such events.

The second double-blind randomized study of D-amphetamine SR enrolled subjects with current cocaine and heroin dependence.[45] The same escalating dosing regimen previously used[126] was combined with methadone (1.1 mg/kg) in these cocaine- and heroin-dependent participants over 26 weeks. Of 94 participants receiving the first dose, retention was best in the 15- to 30-mg/day group (50% completed) followed by the 30- to 60-mg/day (39%) and placebo (25%) groups. Cocaine intake declined significantly in the 30- to 60-mg/day group compared with the 15- to 30-mg/day and placebo groups. Trends were detected toward greater reduction in heroin use in the 30- to 60-mg/day group. This finding is encouraging with the well-documented adverse effect of cocaine use on methadone treatment.[133,134] Meticulous collection and reporting of cardiovascular

measures in both studies[45,126] indicated minimal medical effects (e.g., blood pressure) and no psychiatric consequences emerged in either study.

More recently, Galloway *et al.* reported results from an exploratory 8-week double-blind randomized clinical trial examining D-amphetamine SR (60 mg/day) versus placebo for treatment of methamphetamine dependence.[135] Compliance with the medication regimen was good (~74% for both groups), and no serious adverse events were reported. Adverse event/side effect rates (e.g., sleeping, anxious, alert, and happier) were similar to those previously reported, and one subject discontinued medication because of insomnia. During the trial, the group administered D-amphetamine SR exhibited fewer withdrawal effects than the placebo group. Similarly, diminution in reported "craving" was greater for the active medication group, although this difference was not statistically significant. However, both groups continued to use methamphetamine at similar rates throughout the trial. Although the trial was carefully designed and implemented, the researchers considered that the dose was low for this chronic methamphetamine–using population. Also, trials demonstrating agonist efficacy for stimulant dependence have reported the greatest effect after longer durations of medication administration; thus a further trial, probably with higher doses and of longer duration, may be warranted. Alternatively, without substantially higher doses, D-amphetamine may not be an adequate agonist for severe methamphetamine dependence. The results described earlier by Mooney *et al.*[119] suggest that direct substitution may be the optimal strategy.

Methylphenidate

There have been several studies of methylphenidate for treatment of cocaine dependence alone or with comorbid conditions, as well as one recent report for treatment of single-diagnosis amphetamine dependence. Early case study reports by Khantzian *et al.* suggested benefit of methylphenidate for cocaine dependence, particularly in individuals with comorbid conditions that are treated with this agent.[136] This spurred development of Khanztian's conceptualization of "self-medication."[137] In contrast, opposite findings were reported in a subsequent study.[138] Grabowski *et al.* reported no benefit from a dosing regimen that included an IR dose of 5 mg upon awakening followed by 40 mg SR methylphenidate (total 45 mg/day).[139] Arguably, the dose was inadequate with the rather heroic history of cocaine intake of the subjects. Indeed, the most commonly reported side effect was jitteriness, with no reports of positive mood after medication ingestion. Levin *et al.*, reporting an open trial, described some benefit of methylphenidate for cocaine abuse in individuals also diagnosed with ADHD.[140] Providing some clarification in this dual-diagnosis population, a recent double-blind report suggested that, although there was no significant difference overall between placebo and methylphenidate subjects, those whose ADHD symptoms improved (presumably because of medication) exhibited reduction in cocaine use.[141] Schubiner *et al.* compared placebo and thrice-daily methylphenidate (90 mg/day) and found no reductions in cocaine use in a dual ADHD/cocaine-dependent population.[142] Tiihonen *et al.* reported diminution in amphetamine use in single-diagnosis subjects receiving a terminal dose of 54 mg/day of methylphenidate while interestingly reporting worsening in a parallel arm that received 15 mg of aripiprazole.[143] The finding of methylphenidate efficacy in an amphetamine-dependent, as opposed to a cocaine-dependent, population may clarify direction for research in terms of matching candidate medication with abused drug. Alternatively, the somewhat higher doses or long study duration (20 weeks) may be the critical determinants, and thus methylphenidate might be revisited for low to intermediate severity of cocaine use.

Modafinil

Multiple trials have also investigated modafinil, and it was suggested to have potential benefit for stimulant dependence in two case reports. Malcolm *et al.* reported several cases in which administration of other stimulants had proven ineffective for stimulant abusers but for whom modafinil (400 mg/day) produced benefit.[144] Interestingly, two of the responding patients had concurrent ADHD diagnosis; modafinil itself has modest benefit in the treatment of ADHD alone.[145] Similarly, Camacho and Stein reported some benefit of modafinil (400 mg/day) for amphetamine dependence in a patient who had a concurrent diagnosis of social phobia.[146]

In an open trial, Dackis *et al.* described benefit of modafinil in cocaine users who received 200 or 400 mg of modafinil compared to placebo.[107,147]

They reported 48% abstinence in subjects receiving active medication. Following up on this work, Dackis *et al.* reported significantly more abstinence in the modafinil, compared to the placebo, group with 43% versus 24% benzoylecgonine-negative screens, respectively.[148] These positive results were, of course, worth pursuing, although the study suffered from the fact that on entry the group receiving modafinil had lower rates of positive urine screens, which persisted throughout. No serious adverse events emerged.

From the perspective of administering a medication that would attenuate methamphetamine withdrawal symptoms, McGregor *et al.* compared treatment as usual to mirtazapine (60 mg/day) and modafinil (400 mg/day).[149] This is distinct from an agonist maintenance approach. While noting limitations, the researchers presented important findings for this residential population, noting greater energy, wakefulness, and other benefits of an agonist-like drug in those receiving modafinil than in those taking mirtazapine. Both agents were more effective on several dimensions when compared to a retrospective treatment control group.

Shearer *et al.* recently described an excellent double-blind randomized trial of modafinil (200 mg/day) for methamphetamine dependence, again in a difficult and heterogeneous population.[150] Use of 200 mg versus greater doses was dictated by the absence of difference in previous studies. The authors justifiably rationalized that, with available data, risk should be reduced by using the lower dose. Overall, there was no significant difference between the placebo and modafinil groups during the study. In a more refined analysis that addressed the important issue of compliance rates, Shearer *et al.*[150] found a modest group by time effect for modafinil.

McElhiney and collaborators examined CBT plus up to 200-mg modafinil in a therapeutically complex population, human immunodeficiency virus–positive males using methamphetamine.[151] This single-blind study found some benefit for some subjects. These authors specifically note that benefit was more likely to accrue to those meeting abuse rather than dependence criteria.

Most recently Anderson *et al.* reported a multisite study of modafinil for treatment of cocaine dependence.[152] Placebo, 200 mg, and 400 mg of modafinil were compared over a 12-week period. Using a novel presentation, "Average weekly percent Cocaine Non-Use Days," the initial analysis showed little difference between placebo and medication. However, reanalysis with separation of population subsets, cocaine with or without alcohol dependence, indicated some advantage (more nonuse days) in subjects who were not alcohol dependent. Available data suggest that the overall population had moderate cocaine use severity, as reflected by 45–55% nonuse days during a 2-week baseline period. Interestingly, separate data for the alcohol-dependent subjects during the baseline period indicated 50–65% nonuse days. This finding suggests that concurrent alcohol dependence reduced the efficacy of modafinil even in the presence of fewer days of use. Overall, the data suggest that modafinil benefit, when evident, may occur in less severe and less complicated subjects.

Kampman, in a recent review of some agonist-like agents,[153] has argued for the utility of modafinil on the basis of studies of Dackis[107,147,148] and others. Overall, these data, plus the Shearer *et al.* study,[150] combined with the data of McGregor *et al.*,[149] McElhiney *et al.*,[151] and Anderson *et al.*,[152] indicate that modafinil may be an efficacious agent for less severe patients. This finding would seem to bolster the argument for a continuum of agents and parallels the recommendation below that amphetamine analogues or their equivalent may be the best option for the most severe subset.

Bupropion

Given its profile of action, clinical investigators considered bupropion a plausible candidate for the treatment of stimulant dependence. As previously noted, more recent results of human laboratory evaluations were equivocal. Best representing its potential role in treatment of stimulant dependence is a report by Elkashef *et al.* describing a rigorously conducted, multisite, randomized double-blind trial.[154] As has been common in most pharmacotherapy trials, there was no difference in retention (overall 52% at 12 weeks) for the group receiving placebo and the group receiving a terminal maintenance dose of 300-mg bupropion. There was a trend and modest difference between the two bupropion and placebo groups on the primary outcome, diminution in amphetamine-positive urines, favoring bupropion. Reflecting the issue of selecting pharmacotherapy on the basis of severity, the authors noted that lower methamphetamine use was associated with a

somewhat improved outcome as a function of bupropion. In another secondary analyses, an interesting finding was that, in a subgroup with less (rather than greater) depression, greater effect was noted pointing to the complexity of treatment in dual-diagnosis cases. Other analyses indicated no effect for craving, human immunodeficiency risk, or tobacco use.

L-Dopa/carbidopa

To the extent that enhancement of DA is critical for an agonist-like medication, the notion of replacement and stabilization is captured by the strategy of administering L-dopa/carbidopa, the commercially available agent for Parkinson's disease (Silverman, personal communication, 1997). We conducted three studies with this DA precursor. Mooney *et al.* described two of these, including a safety and a dose-ranging trial.[155] Although there was clear evidence of safety, there was little evidence of behavioral change resulting from administration of L-dopa/carbidopa in the usual therapeutic range. However, in the third study using similar doses, Schmitz *et al.* combined a robust behavioral intervention with L-dopa/carbidopa versus placebo and reported benefit of the active medication.[156] The combined results indicate that agonists with narrow and specific action might best be reserved for special circumstances or therapeutic approaches.

Benefits of agonist treatment

The potential benefits of agonist-like pharmacotherapy are readily summarized and parallel those with nicotine or opiate replacement. As implied by the designations replacement or substitution, the medication has core biological effects similar to the abused agent. However, dose is lower and stable and thus unlikely to precipitate adverse behavioral or biological events. SR preparations maintain medication level and minimize the peaks and troughs of commonly used routes of abuse. This characteristic eliminates the "highs" that produce aberrant behavior and the bolus effects likely to produce cardiovascular or other problems. Thus, stabilization of both behavior and biology are outcomes. As clearly demonstrated with opioid replacement, for which the most extensive data are available, reductions in abstinence-related behaviors and symptoms, including drug seeking and drug taking, can dramatically reduce illicit drug use. Abstinence-related events, such as depressed mood or anhedonia, eating disturbances, lethargy, and myriad other characteristic common or idiosyncratic responses, may also be attenuated.

As with other agonist approaches, reversal of broader patterns may or may not occur. There should be no expectation that stimulant agonists will reduce abuse of other drugs unless the drug use is clearly linked to stimulant abuse. For example, those using sedatives, including alcohol, to attenuate jitteriness or offset effects of stimulants might reduce supplemental drug use when stimulant abuse is effectively treated. Similarly, treatment of heroin or cocaine use in speedball users may lead to some reduction in use of the other agent, although research data are equivocal.[45,133,134,157] Also, the medication cannot directly influence criminal activity or reverse deficits in social skills, education, or employment status. However, stable pharmacotherapy may allow patients in need of such support to be more amenable to therapy focused on social skills, relapse prevention, and other essential behavioral change.

Minimizing risks in therapeutics

All drug/medication administration has risks, usually related to dose and preparation. From the perspective of agonist-like pharmacotherapy, two sources of risk are of particular concern. Cumulative data suggest that, of less concern, is the possibility of psychiatric symptoms caused by the medication itself. The more problematic conundrum stems from possible continued abuse of illicit stimulants (or other drug use, including over-the-counter agents) during a course of pharmacotherapy. Because, on average, substantial reductions in use of the abused stimulant emerge gradually, the period of early dosing may entail the greatest risk. This is not different from pharmacotherapy for other psychiatric conditions (e.g., depression), including substance abuse disorders.

The few double-blind trials of amphetamine analogues for cocaine dependence have been particularly rigorous and carefully monitored side effects, including the use of frequently repeated electrocardiograms. Blood pressure and heart rate effects were nominal with administration of D-amphetamine SR,[126,135] D-amphetamine IR,[132] methamphetamine

SR,[119] or the combination of methadone and D-amphetamine SR in dual-dependence subjects.[45] Multiple reports cited in the foregoing examining D-amphetamine administration for amphetamine abuse and dependence, typically in community-based clinics, did not report serious adverse medical events in diverse populations (see Ref. 41 for review); however, monitoring was less rigorous. In all studies there is the possibility that side effects may have precipitated dropout for some subjects. Using cardiovascular risk as an example, it is clear that the crucial issue concerning the agonist-like conceptualization of pharmacotherapy for stimulant dependence is whether these risks can be substantially reduced or eliminated with a stable regimen; data presented suggest a favorable risk–benefit ratio.

In discussion of whether agonist-like therapy produces or exacerbates cognitive or psychiatric effects commonly attributed to chronic stimulant abuse, it is critical to distinguish differences in dose, preparation, and regimen compared to those of stimulant abuse. Interestingly, a recent report by Benedict *et al.* indicated trends toward improved cognitive function in a population with known pathology (multiple sclerosis) after L-amphetamine administration, which demonstrates palliative benefit for one type of damage.[158] Also, chronic administration with SR amphetamine preparations enhances function in those with ADHD. With the potential cognitive-enhancing properties of agonist agents and uncertain or modest results from some controlled studies of cognition in the aftermath of severe stimulant abuse and dependence,[24] it appears that controlled, stable use of the agonist-like strategy would have limited risk. Likewise, elicitation or augmentation of psychosis is not likely with agonist-like medications. Consistent throughout the agonist pharmacotherapy literature is the extremely low frequency of such events during the course of a monitored regimen, including patients actively treated for other serious disorders (e.g., schizophrenia).[129]

Careful management is essential and can minimize risks. As proposed, agonist-like therapy entails comparatively low, stable stimulant doses compared to patterns of abuse. As with treatment of any substance abuse disorder, careful screening and periodic monitoring of medical and psychiatric conditions are critical to minimizing untoward events. This perspective is substantiated in the spectrum of studies ranging from chart reviews, through community clinic interventions, to randomized clinical trials that have reported few adverse events.

Treatment strategy for agonist regimens

On the basis of the preceding clinical data, we offer the following guidelines for future studies and use of agonist-like medications. The choice of medication should be based on several factors. First, rigorous medical and psychiatric examination should be conducted, paying special attention to the presence of mood, psychotic, and cardiovascular disorders, as well as previous use and experience with agonist-like agents. Each of these queries will help to determine whether agonist-like medications are appropriate. Also, the severity of stimulant abuse should be taken into account. Clinical data suggest that less robust medications (e.g., L-dopa, bupropion, and modafinil) may be appropriate for casual-to-moderate stimulant abusers, and a powerful monoamine releaser (e.g., amphetamine analogues) may be more appropriate for those with severe stimulant abuse or dependence (Table 2). Furthermore, SR agonist preparations should be used because they minimize the potential for abuse of the medication. These preparations also allow once- or twice-daily dosing, a feature that increases medication compliance. Regardless of the medication preparation, infrequent (e.g., one to two times daily) administration is advantageous, because there exists an inverse relationship between the number of daily dosing requirements and medication compliance.[119]

Overall, the data indicate that higher doses of agonist-like medications for stimulant dependence more effectively reduce drug use than lower doses, and thus the findings parallel the opiate agonist literature. For example, we have found that 60 mg/day of D-amphetamine reduces cocaine use to a greater extent than a 30-mg/day dose.[45,126] As noted in the clinical section, many clinical reports suggest that 60 mg/day or more of D-amphetamine may be optimal. This premise may also apply to methylphenidate,[101,139,143] although the dose-dependent nature of modafinil has been debated.[106–108,150,152] Also, effective doses of agonist-like medications will most likely be greater than doses commonly used for other indications. For instance, doses up to 60 mg/day of D-amphetamine are recommended for ADHD treatment, whereas doses at or above this range seem

Table 2. Recommendations for agonist administration

Low severity	Moderate severity	High severity
L-Dopa/carbidopa	Modafinil	D-Amphetamine (SR prep.)
Bupropion	Methylphenidate	*Lisdexamfetamine
Modafinil	*DA/5-HT/NE agonists	*Methamphetamine (SR prep.)
	*Medication combinations	*DA/5-HT/NE agonists
		*Medication combinations

Severity or persistence of drug seeking and drug taking may determine relative utility or efficacy of particular agents or classes of agents for treatment. Accumulating clinical data indicate that some agents might be most useful for one or another category. This continuum should also provide guidance when designing a sequential medication strategy. Asterisks indicate the predicted utility and categorization of agents for which there are no, or inadequate, clinical data.

to be the most effective to reduce cocaine use (e.g., Refs. 45, 120, 124, and 159). The neural basis for this phenomenon is not fully understood; however, some evidence suggests that chronic stimulant abuse decreases sensitivity to dopaminergic medications.[54] Collectively, these data indicate greater effectiveness of agonist medication dosing at the high end of the recommended range.

Time to the maximal reduction in drug use will vary and may take several months. In our previous studies, there was a 2- to 3-month delay between D-amphetamine administration and substantial reductions in cocaine use.[45,126,159] This delay between stimulant initiation and reduction in drug use was also clearly demonstrated by Tiihonen *et al.*, where 18 weeks of administration with methylphenidate was required to significantly reduce amphetamine use.[143] Similarly, the maximum reduction in cocaine use with modafinil was not immediate, developing throughout the study.[148] These findings parallel the opiate literature, indicating maximal benefit for agonist-like medications after several months of administration (e.g., Ref. 160). Nevertheless, it is clear that further investigation is needed to clarify dosing and duration parameters. For example, Grabowski *et al.* used an escalating dose approach that probably delayed maximum benefit with D-amphetamine observed in months 2 and 3.[45,126] In contrast, Mooney *et al.* reported relatively rapid benefit with methamphetamine SR,[119] as did Merrill and Tetlow with D-amphetamine.[124]

Future directions

Available novel medication preparations

Despite documented safety and efficacy, and absence of diversion in studies to date, a major concern among some clinicians and clinical scientists is that treatment-seeking individuals will abuse prescribed medication. An agonist preparation with enhanced abuse-resistant features would help to alleviate this concern. A recent advance in drug delivery technology has resulted in an amphetamine formulation possessing these attributes. Lisdexamfetamine (LDX) is an amphetamine prodrug approved by the FDA for the treatment of ADHD. This medication consists of D-amphetamine covalently bonded to the amino acid lysine. After oral administration, the enzymatic environment of the gastrointestinal tract and circulatory system converts the prodrug (LDX) to the active drug (D-amphetamine) by enzymatic cleavage of lysine from amphetamine.[161,162]

This medication has several advantageous features for use as an agonist-like preparation. After oral administration, the kinetics of the enzymatic reaction are such that the medication has a slow onset and long-lasting efficacy similar to that of an SR amphetamine preparation[163,164]; this serves to reduce abuse potential. Related, LDX may have decreased abuse potential if administered via other routes (e.g., intranasal), because the rate of conversion of LDX to active medication is similar with its oral or intranasal administration,[161,162] which is much unlike the case for IR D-amphetamine when administered intranasally. Furthermore, this medication may have properties reducing the likelihood of overdose, because the rate-limiting factor in prodrug activation is the concentration of enzymes available to cleave lysine and amphetamine.[165]

We recently implemented a clinical trial investigating a CBT protocol plus LDX (70 mg/day; 12 weeks) versus placebo for treatment of single-diagnosis cocaine dependence. The primary

outcomes are (1) changes in cocaine use, as operationalized by the proportion of cocaine-positive urine screens; (2) the proportion of individuals achieving sustained abstinence; and (3) the longest sustained period of abstinence. Secondary outcomes include drug craving and impulsivity. We hypothesize that LDX should effectively treat cocaine dependence with efficacy similar to that of D-amphetamine SR and exhibit an enhanced risk–benefit profile. In the future, the ability of LDX to attenuate stimulant reinforcement should be determined with human laboratory studies. Also, medication trials should investigate LDX for treatment of methamphetamine dependence, or LDX plus methadone for treatment of dual cocaine/opiate dependence.

Mixed DA/5-HT/NE agonists or medication combinations

Another promising direction is with use of single medications or combinations of medications to produce broad activation of DA, 5-HT, and NE systems. Most agonist studies have focused on the importance of the DA system; however, recent research suggests that the 5-HT system should also be targeted[58,65,166]; the rationale for examining medications that enhance NE is less clear but supported by some data.[50,167] We contend, and the data suggest, that pharmacotherapies with broad action at DA, 5-HT, and NE should be pursued.

This strategy may have several advantages. First, pharmacotherapies that activate DA, 5-HT, and NE systems will be more likely to mimic the effects of the abused drug versus more selective medications, thus fulfilling the requirement of similarity in neurochemical effects and some, but not all, subjective and behavioral effects as the abused drug. The involvement of DA, 5-HT, and NE systems in the neurochemical effects of cocaine and methamphetamine supports use of pharmacotherapies with a broad action.[50] Also, it is important for agonist-like pharmacotherapies to possess decreased abuse liability versus the abused stimulant. Preclinical studies reported that the appetitive effects of DA agents are decreased by 5-HT[116]; thus, abuse liability should be minimized with a pharmacotherapy targeting both systems. Furthermore, some adverse consequences associated with chronic stimulant use may be minimized. Rothman *et al.* have proposed a dual-deficit hypothesis for stimulant dependence, hypothesizing that both 5-HT and DA deficits contribute to effects, such as anhedonia, depression, obsessional thoughts, decreased impulse control, craving, and relapse.[65] Use of pharmacotherapies with broad action should alleviate these effects and reduce drug use.

Both preclinical and clinical studies support pursuit of this strategy. For example, the combination of the DA releaser phentermine and 5-HT releaser fenfluramine reduced cocaine self-administration in animals, without self-administration of the combination, suggesting minimal abuse liability.[168] Similar findings were reported with the DA/5-HT/NE releaser PAL-287.[116] In line with the dual-deficit hypothesis, an open-label clinical study found some decrease in withdrawal symptoms from the combination of phentermine and fenfluramine.[169] The most influential clinical support for this strategy was reported by Mooney *et al.*, where an SR preparation of the DA/5-HT/NE releaser methamphetamine nearly eliminated cocaine use, with excellent safety and tolerability.[119]

Although further development of methamphetamine might be problematic, this proof-of-concept study clearly directs attention to the need for investigation of pharmacotherapies with broad action. This strategy could be pursued with single medications, such as the DA/5-HT/NE releaser PAL-287, or related compounds. Alternatively, combinations of FDA-approved stimulants (e.g., D-amphetamine) and serotonergic medications (e.g., selective serotonin reuptake inhibitors [SSRIs]) might be effective. Another intriguing possibility is the prodrug phendimetrazine.[170,171] Phendimetrazine is metabolized to phenmetrazine, a DA/5-HT/NE releaser that has been shown to selectively attenuate cocaine versus food reinforcement.[170,171] Phendimetrazine may provide the advantages of a prodrug, like those described for LDX, plus the benefit of broad action at DA, 5-HT, and NE systems. The human behavioral pharmacology laboratory is an ideal environment to test the efficacy of these pharmacotherapies, followed by subsequent medications trials.

Sequential medication strategy

Given some concerns about long-term agonist exposure, a treatment strategy that may serve to

effectively treat stimulant dependence, yet minimize exposure to robust agonist medications, is a sequential medication approach. This strategy has been advocated for opiate dependence[4] and entails administration of a robust medication, followed by less robust agents or those possessing alternate mechanisms of action. Our 8-week feasibility study consisted of stabilization with D-amphetamine SR (30 mg/day) or placebo for 4 weeks and then transition (weeks 5–8) to the DA medication L-dopa/carbidopa, SSRI fluoxetine, or continued D-amphetamine treatment.[159] Subjects administered placebo continued to receive placebo during the second phase, and all subjects received weekly CBT for the duration of the study. The study demonstrated safety and feasibility, with excellent medication tolerance and compliance, no difficulty with medication transition, as well as superb retention. Because this was a feasibility study, there was not adequate power to detect medication effects between treatment groups; however, those given D-amphetamine throughout the trial exhibited continued reductions in cocaine use. Lesser effects were found for L-dopa, whereas an increase in cocaine use emerged with the transition to fluoxetine alone. In all, this study demonstrated feasibility and suggests further pursuit of this strategy. Future efforts should include a longer duration of stabilization with D-amphetamine (60 mg/day), followed by L-dopa, perhaps in combination with a more robust behavioral therapy, such as contingency management. Ultimately, successful patients might subsequently be given DA antagonists, perhaps followed by a medication-free state, with the goal of long-term abstinence from cocaine.

Summary

This review has addressed the problems of stimulant abuse/dependence and data supporting the agonist-like approach, including consideration of risks and benefits. We propose that medication development and therapeutics should proceed based on the continuum of severity for the disorder and robustness of therapeutic agent effects.

Preclinical findings and conclusions

Not surprisingly, the preclinical data provide important reminders of the multifaceted neurochemical and behavioral actions of commonly abused stimulants and the substrates on which they act. With this complexity, consideration must be given to a spectrum of medications with various action at DA, 5-HT, and NE systems. Notwithstanding gaps in knowledge, our understanding of these systems dictates that agents with broad action will be essential to ameliorate the consequences of long-term abuse, including those associated with abstinence. At the preclinical level, the neurochemical and behavioral similarities of a candidate agent to the abused drug should determine further development as an agonist-like agent. The ability of a medication to attenuate stimulant-evoked behavior should provide additional guidance.

Human laboratory findings and conclusions

These data build upon and inform preclinical research while illustrating the complex interactions between stimulant abuse, medications, and human behavior. Here, measurements of self-reported "subjective effects" come into play. The subjective effects of stimulants should be similar between individuals; however, there are likely to be differences, some subtle, some not, depending on the history of drug use. For example, experienced users may be able to better articulate subjective liking, dislike, or side effects when compared to those with little previous use. Conversely, experienced users may also be less responsive to a "mild" relatively selective agent, thus suggesting less benefit as an agonist-like medication. In addition, a medication may reduce some self-reported features, for example, craving or specific abstinence symptoms, whereas it may not reduce actual drug taking. Thus, the combined use of self-administration paradigms and subjective measures in the human laboratory environment probably provide critical data in terms of medication development. Again, the goal is achieving a balance between reduction in drug use and minimization of risk.

Clinical trials findings and conclusions

The level of monitoring and rigor in evaluations of agonists in clinical settings has varied widely. There are three converging lines of clinical evidence aside from human laboratory studies. One entails the clinical reports of efficacy, generally from U.K. substance abuse treatment programs. A second comprises the community-based clinical trials, several conducted

in Australia. The third entails unusually rigorous clinical trials, usually in specialized research clinics in the United States. The body of literature that has accumulated over the last two decades supports the efficacy of agonist administration, generally amphetamine analogues but also agents, such as L-dopa/carbidopa, bupropion, methylphenidate, and modafinil. Some agents, for example, modafinil, may not possess traditional prototypic stimulant (e.g., cocaine) mechanisms but produce some of the behavioral effects (e.g., wakefulness, attentiveness). Overall, among the many and varied agents examined, agonist-like medications have produced the most promising results in patients.

Overall summary

Stimulant abuse/dependence should be examined with the view that there may be recurring episodes of variable severity, that return to use might be diminished by agonist-like medications, and that in any case a range of medications should be available. Although stimulant abuse and dependence have substantial risks, ample data indicate that well-monitored regimens of stimulants for ADHD, narcolepsy, as well as substance abuse treatment, are relatively safe and have a favorable risk–benefit ratio. Conversely, although there has been extensive examination of other medications, such as anticonvulsants or antagonists (usually antipsychotics), results have been disappointing and, like any medication, these agents have significant risks and adverse consequences as well. With the wide variability in stimulant use patterns and their effects, medication administration should be predicated on a continuum of severity. No single agent will be the panacea for the spectrum of patients. This parallels the differential response to SSRIs across depressed patients; it is poorly understood but clinically apparent. The data and conceptualization suggest that a range of agonist-like agents, from modest to robust, should be explored. At times, stimulant abuse/dependence may also require combinations of medications. Further, variation in severity of stimulant abuse/dependence, individual differences, and at times collateral conditions, whether acute (e.g., psychosis) or preexisting and enduring (e.g., depression), may dictate instances where several classes of medications will be essential for treatment, either briefly or for the long term. In sum, development of a range of agonist-like agents will result in better treatment for stimulant dependence.

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Conflicts of interest

The authors declare no conflicts of interest.

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