Circumspective

Agonist Medications for the Treatment of Cocaine Use Disorder

S Stevens Negus*[1] and Jack Henningfield[2,3]

[1]Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA, USA; [2]Pinney Associates, Bethesda, MD, USA; [3]Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Cocaine addiction is a persistent and insidious public health problem (Pomara *et al*, 2012). Despite evidence for sustained prevalence, clinical harm, and demand for treatment, the Food and Drug Administration (FDA) has yet to approve any pharmacotherapy for its treatment. 'Agonist' medications such as amphetamine maintenance have emerged as one intriguing but controversial class of candidates, and this Circumspectives Article presents pros and cons of agonist medications for treatment of cocaine-use disorder. Evidence in favor of agonist medications will be presented by Dr Steve Negus. Dr Negus has contributed for more than 20 years to research on medications development for drug-abuse treatment, and he published early preclinical data supporting efficacy of amphetamine maintenance to reduce cocaine self-administration. Regulatory challenges to the use of agonist medications will be presented by Dr Jack Henningfield. Dr Henningfield also has decades of experience in preclinical and clinical evaluation of both abuse potential of novel drugs and utility of candidate treatments. He was involved in the research and regulatory processes that led to FDA approval of various nicotine agonist therapies and of buprenorphine as an analgesic and agonist therapy.

EVIDENCE IN FAVOR OF AGONIST MEDICATIONS TO TREAT COCAINE-USE DISORDER (STEVE NEGUS)

Amphetamine maintenance reduces cocaine-taking behavior in rats, nonhuman primates, and humans (Howell and Negus, 2014).

My research on medications development is founded on the premise that consideration of any medication for any

*Correspondence: Dr SS Negus, Department of Pharmacology and Toxicology, Virginia Commonwealth University, 410 North 12th Street, Richmond, VA 23298, USA, Tel: +804 828 3158, Fax: +804 828 2117, E-mail: ssnegus@vcu.edu

indication depends initially on evidence for therapeutic efficacy. Absent that evidence, little else matters. However, as evidence for efficacy accumulates, then secondary issues related to safety and deployment become increasingly relevant. My advocacy for consideration of agonist medications to treat cocaine-use disorder stems from the growing body of preclinical and clinical evidence for their therapeutic efficacy.

DEFINITION OF DRUG-USE DISORDERS AND METRICS OF THERAPEUTIC EFFICACY

In considering this evidence, it is useful to begin by offering definitions both for the disease and for metrics of therapeutic efficacy. Substance-use disorders are defined by a maladaptive allocation of behavior toward acquisition and use of drugs and away from behaviors maintained by alternative reinforcers (Ahmed *et al*, 2013; American Psychiatric Association, 2013; Banks and Negus, 2012; Heyman, 2009). From this perspective, treatment efficacy can be defined both by reductions in drug-taking behavior and also by reallocation of behavior toward healthy alternative activities. Pharmacotherapy can promote this behavioral reallocation by multiple mechanisms (Grabowski *et al*, 2004; Howell and Negus, 2014; Rothman *et al*, 2002; Stoops and Rush, 2013). Perhaps the simplest and most intuitive mechanism is an 'antagonist' approach that prevents the abused drug from reaching the brain (eg, with vaccines that promote rapid peripheral metabolism of the abused drug) or from reaching target receptors within the brain (eg, with receptor antagonists). The μ-opioid receptor antagonist naltrexone, which is approved for treatment of opioid-use disorders, is one example of an antagonist medication that can have high therapeutic efficacy and safety under appropriate conditions. However, compliance has been a significant obstacle to the use of naltrexone (Comer *et al*, 2007) and antagonist approaches have not yet succeeded as viable pharmacotherapies for cocaine-use disorder (Gorelick, 2012; Grabowski *et al*, 2000; Haney *et al*, 2001).

'Agonist' medications offer a different approach. Agonist medications are drugs that share pharmacodynamic me-

chanisms of action with the abused drug but that usually have distinct pharmacokinetic characteristics (eg, enteral bioavailability, slow onset of action, long duration of action) (Grabowski *et al*, 2004; Rothman *et al*, 2002). The overlap in pharmacodynamic mechanisms endows agonist medications with at least three important attributes. First, maintenance on agonist medications can attenuate reinforcing effects of the abused drug by competing with the abused drug for its receptors and/or by producing cross tolerance to effects of the abused drug at those receptors (Bauer *et al*, 2014; Kreek *et al*, 2002). Second, agonist medications have high probability of functioning as effective reinforcers in patients, and as a result, their delivery in a clinical context can be leveraged to promote compliance and reinforce other desirable behaviors (Preston *et al*, 2000). Third, agonist medications can alleviate withdrawal signs that contribute to relapse (Koob, 2009; Negus and Banks, 2013). The pharmacokinetic attributes of agonist medications enable their use by safer routes of administration (eg, oral and sublingual) than the intravenous or smoked routes common in drug abuse. In addition, slow drug onset can reduce abuse potential (Lile, 2006) and long duration of action can reduce the frequency of required treatment and also reduce problematic neuroadaptations to the severe oscillations in drug levels that often occur with drug abuse (Kreek *et al*, 2012). Of course, agonist medications can also produce undesirable effects similar to those of the abused drug, and in the context of addiction treatment, abuse liability is an especially prominent concern. Nonetheless, agonist medications have been successfully developed and deployed, and examples include oral methadone for the treatment of opioid dependence and nicotine formulations for the treatment of tobacco dependence. It was the relative success of these medications for treatment of addiction to other drugs that stimulated initial research on potential of agonist medications to treat cocaine-use disorder.

EVIDENCE FOR THERAPEUTIC EFFICACY OF AGONIST MEDICATIONS TO TREAT COCAINE-USE DISORDER

Cocaine functions as an inhibitor of dopamine, norepinephrine, and serotonin transporters, and its effects on dopamine are most strongly implicated in its abuse liability (Johanson and Fischman, 1989; Koob, 1992; Ritz *et al*, 1987). Consequently, drugs acting as dopamine uptake inhibitors, dopamine releasers, or dopamine receptor agonists have all been evaluated as candidate agonist medications for treatment of cocaine abuse (Grabowski *et al*, 2004; Herin *et al*, 2010; Rothman *et al*, 2002; Stoops and Rush, 2013). Of these, the most promising effects have been obtained with dopamine releasers in general, and with amphetamine maintenance in particular. In a series of early preclinical studies, we found that chronic amphetamine treatment decreased cocaine self-administration in rhesus monkeys responding under several different schedules of cocaine reinforcement, including a 'choice' procedure in which monkeys choose between cocaine injections and food pellets (Figure 1) (Negus, 2003; Negus and Mello, 2003a, b). These initial findings have been replicated and extended by us (Banks *et al*, 2013b), by other investigators working with other schedules of cocaine self-administration in nonhuman primates (Czoty *et al*, 2010; Czoty *et al*, 2011), and by investigators working with various schedules of cocaine self-administration in rats (Chiodo *et al*, 2008; Thomsen *et al*, 2012). In addition, amphetamine maintenance decreased cocaine *vs* money choice in human laboratory studies (Greenwald *et al*, 2010; Rush *et al*, 2010), and cocaine use by patients in placebo-controlled double-blind clinical trials (Grabowski *et al*, 2001; Mariani *et al*, 2012). Finally, recent meta-analyses of clinical studies have highlighted agonist medications in general, and amphetamine maintenance in particular, as superior in efficacy to many other drug classes as candidate medications for treatment of cocaine
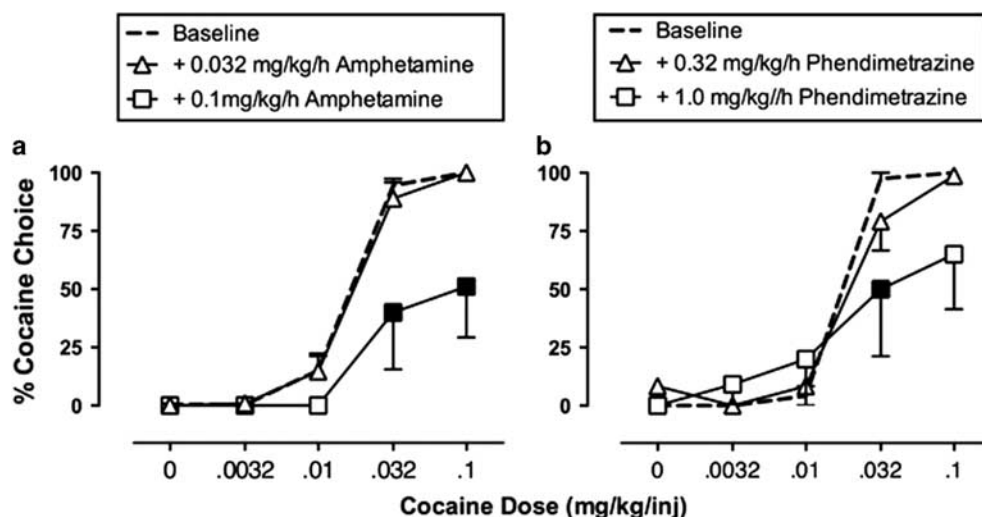

Figure 1 Maintenance on amphetamine (a) or phendimetrazine (b) decreases cocaine *vs* food choice in rhesus monkeys. During experimental sessions, monkeys (*N* = 4–6) could choose between a single food pellet and one of a series of increasing cocaine doses. Each graph shows the percentage of cocaine choice on the Y axis as a function of the available cocaine dose on the X axis. Under baseline conditions, increasing unit doses of self-administered cocaine maintained a dose-dependent increase in cocaine choice. Filled points show significant decreases in cocaine choice produced by continuous 14-day treatment with intravenous amphetamine or phendimetrazine. Adapted from Banks *et al*, 2013b.

dependence (Amato et al, 2007; Amato et al, 2011; Castells et al, 2010; Minozzi et al, 2008; Pani et al, 2011a; Pani et al, 2011b).

In an effort to improve both efficacy and safety, more recent research has compared effects of amphetamine with effects of other monoamine releasers, or with other classes of candidate agonist medications. This work has suggested three general conclusions. First, pharmacological selectivity to release dopamine > serotonin appears to be one determinant of monoamine releaser efficacy to reduce cocaine choice with minimum side effects (Banks et al, 2011; Haile et al, 2010; Mooney et al, 2009; Negus et al, 2009; Negus et al, 2007; Rothman et al, 2005). Thus, effects of amphetamine can be mimicked by other dopamine-selective releasers such as phenmetrazine or methamphetamine, but not by serotonin-selective releasers such as fenfluramine. Second, prodrugs for amphetamine and phenmetrazine can also decrease cocaine choice (Banks et al, 2013a; Banks et al, 2013b). For example, lisdexamfetamine is a Schedule II prodrug for amphetamine that produces an amphetamine-like reduction in cocaine choice [Banks ML, Hutsell BA, Blough BE, Poklis JL, Negus SS (submitted). Effects of 7-day lisdexamfetamine treatment on choice between cocaine and food in rhesus monkeys.]. Similarly, phendimetrazine is a prodrug for phenmetrazine that also reduces cocaine choice (Figure 1), and the Schedule III status of phendimetrazine reduces barriers to its use by physicians. More generally, the efficacy of these prodrugs is relevant insofar as they may have lower abuse liability than their active metabolites. Finally, studies in both animals and humans have suggested that amphetamine and related monoamine releasers may be safer and/or more efficacious than other classes of candidate agonist medications including both monoamine uptake inhibitors and dopamine receptor agonists (Czoty et al, 2013; Grabowski et al, 2004; Howell and Negus, 2014). However, the generality and underlying basis for this apparently higher safety/efficacy of dopamine-selective monoamine releasers has not been explored.

CAVEATS AND CONCLUSIONS

The FDA can approve drugs either to manage diseases (eg, antihypertensives) or to cure them (eg, antibiotics), and agonist medications for substance-use disorders are examples of the former. In addition, the primary endpoints in preclinical and clinical trials of anti-cocaine medications focus on measures of cocaine consumption, and reductions in cocaine consumption during agonist-medication maintenance can be dramatic (Negus and Mello, 2003b). However, some cocaine use often persists, and clinical acceptance of agonist medications will ultimately depend on their effectiveness not only to reduce cocaine use but also to increase the numbers of drug-free days and retain participation in treatment as has been demonstrated in opioid agonist therapy (eg, see FDA, 2002). A final important caveat with agonist medications is concern over side effects that include abuse liability and cardiovascular effects. Prevailing data suggest that agonist medications such as amphetamine produce surprisingly weak evidence for abuse potential or cardiovascular risk in cocaine abusers (Comer et al, 2013; Grabowski et al, 2004; Lane et al, 2014; Rush

et al, 2009), but it remains important to weigh therapeutic effectiveness against risk factors and to also consider risks associated with medication diversion to nonpatients.

Despite these caveats, maintenance on amphetamine and related monoamine releasers has displayed greater and more reliable therapeutic efficacy to reduce cocaine consumption than any other type of medication tested to date. Moreover, the translational consistency of amphetamine maintenance to reduce cocaine-taking behaviors across multiple species and experimental procedures has been striking. In my view, the force of evidence for therapeutic efficacy suggests that secondary issues related to safety and deployment now warrant serious consideration. I would further submit that reasonable strategies are available (eg, use of prodrugs) to mitigate many of the concerns related to these secondary issues.

CHALLENGES TO THE APPROVAL OF AGONIST MEDICATIONS FOR TREATMENT OF COCAINE-USE DISORDERS (JACK HENNINGFIELD)

From the Director of the National Institute on Drug Abuse: Beyond its devastating effects on individual health, methamphetamine abuse threatens whole communities, causing new waves of crime, unemployment, child neglect or abuse, and other social ills (Volkow, 2013).

The use of amphetamine-based agonist therapy for treatment of cocaine dependence has not been established to FDA standards or generally accepted as safe and effective according to a benefit-risk assessment as is increasingly emphasized by FDA, and as consistent with precedent and its statutory obligations (eg, see FDA, 2013b, d; Pina and Pines, 2012). Moreover, as discussed further on, although stimulants vary widely in their risks of abuse, overdose, and other harms, the risks, real and perceived, such as expressed by the National Institute on Drug Abuse (NIDA) Director, Dr Nora D Volkow, will affect the viability of any for approval as agonist therapy. My work on drug regulation recognizes that evidence of therapeutic efficacy is a necessary, but far from sufficient, requirement for approval of a drug for a given indication. Risks, real and perceived, are equally important in determining whether there is a satisfactory benefit-to-risk balance to support approval. If the risks are serious, and the FDA and advisory committees are not convinced that they can be satisfactorily controlled by implementation of a risk management program, then it is unlikely that the drug will be approved for that indication. In addition, there must be sufficient evidence to develop the extensive labeling generally referred to as 'Professional Labeling,' the 'Full Prescribing Information,' or the 'Package Insert', as required by law to provide the extensive and detailed information necessary for safe and effective use (FDA, 2006). Thus, I believe that regardless of evidence for therapeutic effectiveness, it is unlikely that an agonist treatment will be approved within the decade in the United States if ever, because the prime agonist candidate is amphetamine: a drug that is itself of great concern in the United States (eg, see Gerlach et al, 2014; NIDA, 2014a, b, c).

In reality, stimulants vary widely in their risks of abuse and risks associated with their use such that the adverse

consequences of their use and abuse are far worse for cocaine and illicitly manufactured amphetamine products as compared with prescribed pharmaceutical stimulants, but this distinction appears lost on many who are involved in drug control as has been discussed elsewhere (Gerlach et al, 2014). Moreover, as discussed in this commentary, there is no apparent sponsor willing to commit the extensive resources and sustained effort that would be required to develop the science base sufficiently to enable submission of a New Drug Application (NDA), including development of the Full Prescribing Information, to the FDA and be prepared to implement the likely requisite postmarketing risk-management program.

RELEVANT PRECEDENTS

Decades of experience with opioid- and nicotine-based agonist therapy provide both supporters and opponents of such therapies an ample arsenal of data and arguments to support their positions for and against approval of such therapies. From a regulatory perspective, such debates may raise the hurdles for drug approval and slow the review process, because FDA is required to evaluate all credible safety concerns to provide assurance that the drug products it approves are acceptably safe.

Anticipation of a protracted and burdensome regulatory process can dissuade sponsors and potential investors from initiating and then pursuing such drug development. This is not unique to drug-dependence treatments or the approval of drugs that are regulated as controlled substances; however, controlled substances require increasingly diverse and complex studies to evaluate abuse potential, additional documentation in drug application filings (eg, Abuse Potential Assessment), and postmarketing requirements beyond what is typically required of drugs that are not regulated under the provisions of the Controlled Substances Act (CSA) (Calderon and Klein, 2014; Cone et al, 2013; Dart, 2009; Dasgupta and Schnoll, 2009; FDA, 2009, 2010a, 2013a; Leiderman, 2009; Schnoll et al, 2006).

Sodium Oxybate (Xyrem) for Fibromyalgia

The effort to gain approval of sodium oxybate for treatment of fibromyalgia should be sobering for supporters of stimulant agonist therapy. Sodium oxybate is a medicinal form of γ-hydroxybutyric acid that was approved as a Schedule III drug for treatment of narcolepsy in 2002 (Jazz Pharmaceuticals, Inc., 2014). Additional research indicated great promise for the treatment of the frequently devastating and sometimes deadly disease, fibromyalgia. In 2009, FDA convened an advisory committee to address FDA's questions and concerns about this application. Despite what this author believes was very strong scientific support for efficacy and very low real-world risks, the FDA advisory committee voted 20 to 2 against extending approval. (By way of disclosure and basis for his insights, JEH served as an expert on behalf of the sponsor, Jazz Pharmaceuticals, and provided testimony concerning the scientifically documented risks including sexual assault, and the sponsor's Risk Evaluation and Mitigation Strategies (REMS) program to mitigate the risks.) The vote heavily reflected

fears concerning potential abuse and use in sexual assault, despite the fact that rates of abuse of the marketed product were so low as to not be evident in national surveillance monitoring, and neither the FDA nor other experts or organizations had documented the use of the marketed product over the preceding 7 years in sexual assault, except for one potential case that had not been verified by FDA or other experts (Carter et al, 2009; FDA, 2010b). Nonetheless, in the face of the advisory committee vote, the FDA informed the sponsor that it could not approve sodium oxybate for fibromyalgia without additional extensive study and other commitments. FDA provided no assurance that the NDA would ever be approved. Although not earmarked as 'date rape' drugs, amphetamine and like stimulants carry their own baggage as drugs of very serious concern, and the indicated population being dependent and 'abusers' by definition would likely greatly magnify those concerns.

Opioid and Nicotine Agonist Therapies

Two examples concerning the prototypic agonist therapies for opioid and tobacco dependence illustrate additional challenges. In the case of buprenorphine-based therapies, the sponsor of the drug developed and tested dosage forms specifically designed for treatment of opioid use disorders. The sponsor demonstrated remarkable commitment of human and fiscal resources over ∼25 years, often working as a virtual partner with NIDA, to evaluate, develop, and garner FDA approval for these formulations, with no assurance that the product would be commercially successful (Campbell and Lovell, 2012). The many studies supported by the sponsor and NIDA included 'three adequate and well-controlled studies,' and many additional studies that unequivocally demonstrated efficacy, a favorable benefit-risk assessment, and the sponsor's commitment to a costly and extensive risk-management program as described in the NDA (FDA, 2002). In addition, it took the support of the White House Office of National Drug Control Policy, along with support by NIDA and the Substance Abuse and Mental Health Services Administration (SAMSHSA), cooperation with the FDA, and 'Acts of Congress' to create a path for approval and potential office-based use of the product in 2002, and in ensuing years to gradually widen its access via willing treatment providers (Campbell and Lovell, 2012; FDA, 2002).

Nicotine agonist ('replacement') therapies for smoking cessation have been approved since 1985, but with a very narrow indication for smoking cessation and warnings to limit how it is used (PHS Guideline Update Panel L, Staff, 2008). The 1995 approval of nicotine gum for over-the-counter marketing provides a detailed benefit-risk assessment based on a decade of marketing experience and further studies, as well as the postmarketing surveillance and other risk-management program commitments of the sponsor (FDA, 1995). Despite decades of experience, the labeling and warnings have changed relatively little, despite efforts by leading organizations and experts in support of extensions of the use and inclusion of instructions that are predicted to help more people quit smoking (eg, combination use of products such as nicotine gum and nicotine patch, the use of products to reduce rather than cease smoking, and initiation of medication use before smoking

cessation to facilitate cessation) (Carpenter et al, 2013; Fiore et al, 2008; Fucito et al, 2014; Kozlowski et al, 2007). (By way of disclosure and basis for his insights, JEH provided consulting services to GlaxoSmithKline, which was also exploring such extensions of the indication.) The same FDA division that has been hesitant to broaden labeling provisions for nicotine replacement therapy without further evidence to support a benefit-risk assessment, the Division of Anesthesia, Analgesia, and Addiction Products, would be the lead reviewing division of an application for stimulant agonist therapy for cocaine-use disorder. The willingness of FDA and society at large to accept the perceived risks of an amphetamine-based agonist therapy would also be accompanied by the likely assumption that the therapy would not be effective for any more than a minority of those treated. This would be consistent with extensive experience with opioid and nicotine agonist therapy.

THE FDA DRUG-APPROVAL PROCESS EMBODIES CRITERIA UNLIKELY TO BE MET BY AGONIST THERAPY

FDA is charged with assuring that marketed drugs are safe and effective according to a benefit-risk assessment (Table 1 (FDA, 2013b, 2013c, 2013d; Hilts, 2003; Pina and Pines, 2012). Approval of a drug product as safe and effective is in the context of its intended use ('indication'), which includes the population being treated. Approval also includes labeling, which guides conditions of use, provides warning about side effects, and provides information to help healthcare professionals, and patients determine whether it's use is appropriate and whether the benefit-to-risk balance is acceptable. Some drugs and drug classes that carry potentially serious risks are only approved in the context of labeling and restrictions to mitigate those risks and provide conditions to assure safe use. This includes CSA scheduling, other risk-management conditions, and in some cases congressionally required REMS requirements that may include additional premarket study, restrictions on access and use, and extensive postmarket obligations (Dart, 2009; Dasgupta and Schnoll, 2009; FDA, 2009; Leiderman, 2009). For example, buprenorphine products for treatment of opioid dependence are scheduled under the CSA and are subject to REMS (SAMHSA, 2014a). Approval of a methylphenidate transdermal system in 2006 was in the context of risk-management requirements to address concerns, including concerns about abuse liability, posed by the transdermal delivery approach (McCormick et al, 2009).

Although these charges to FDA may seem straightforward, the reality is that it typically requires many years of effort, many millions of dollars, and many studies to evaluate the specific drug product that will be submitted for approval. FDA approval of a category of products, eg, stimulants, is not likely. Thus, the labeling for the specific product must include a scientifically informed basis for dosing recommendations and restrictions intended to assure safe and effective use according to a benefit-risk assessment in the intended population. Studies may include evaluation of the pharmacokinetics and effects in various subpopulations, and in conjunction with other drugs that are likely to be used in the population, as well as in persons with co-morbid disease states commonly occurring in the indicated population.

CAVEATS AND CONCLUSIONS

On the supportive side, as summarized by Dr Negus, there has been good progress in developing the scientific foundation supporting the plausibility that stimulant agonist therapy could ultimately be developed to the point at which science would support an NDA that could be approved as safe and effective. However, all of the work that has been done to date does little more than test the proof of concept. It appears to be far short of what would likely be necessary to develop a credible NDA as summarized in Table 2. Agonist-based treatment of cocaine-dependence/use disorder with amphetamine-type stimulants is long on theory and far short of the evidence that would be required for the candidate product that would be submitted in an NDA. In fact, it is not clear what the specific product entity ('drug substance'), dosage form, or actual drug product to be submitted for approval would be. Nor is there an apparent sponsor willing to provide the likely several years of sustained support to develop and evaluate the product and indication for which approval would be sought, to develop and commit to extensive postmarketing requirements, and to martial a program to garner the broad political support that may be required to facilitate approval and conditions of access that would be necessary to assure success from both a commercial and public health perspective. Unfortunately, the prospects appear better that fibromyalgia sufferers will have the opportunity to benefit from sodium oxybate therapy.

HOW TO MOVE THE FIELD FORWARD (STEVE NEGUS AND JACK HENNINGFIELD)

A substantial and growing body of evidence supports the potential therapeutic effectiveness of amphetamine and pharmacologically related 'agonist' medications for treatment of cocaine-use disorder, but clear obstacles exist to the acceptance and deployment of such medications. In this

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Table I FDA is Charged to Determine the Following as Part of its Evaluation of an Application for Approval of a Drug, Whether the Drug is a New Chemical Entity, or a New Formulation or Clinical Indication of an Already Approved Drug (FDA, 2013c)

1. Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.

2. Whether the drug's proposed labeling (package insert) is appropriate, and what it should contain.

3. Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.

Table 2 What Would be Needed to Develop a New Drug Application for a Plausibly Approvable Stimulant Agonist Product for the Treatment of Cocaine Dependence/Used Disorder?

1. A sponsor with the resources, commitment, and expertise to initiate and execute studies, prepare for meetings with FDA and advisory committees, and ultimately develop an NDA. The sponsor must also be prepared and willing to carry out the postmarketing REMS program likely to cost many millions of dollars per year.

2. Adverse event reporting needs to be done to the standards of what FDA expects in pivotal clinical studies, which is more extensive than is typical in most NIH-supported studies.

3. Identify the candidate drug substance and dosage form with respect to its pharmacokinetic profile and range of doses. If the drug substance is amphetamine, the specific salt or combination needs to be identified. Other potential candidates need to be considered, because they will be suggested by others as possibly better candidates for approval.

4. The development and evaluation of a formulation of the drug that would be expected to facilitate safe and effective use and ideally to mitigate abuse and diversion in this high-risk population needs to be considered, because a formulation that does not enable simple conversion for injection, smoking, or snorting would be more acceptable to the FDA and advisory committees than formulations that are easily adapted for use by nonintended routes.

5. Develop an REMS, which may itself require studies to provide the basis for recommendations for Elements to Assure Safe Use (ETASU), training and accreditation of treatment providers, postmarket surveillance to enable rapid detection of unintended consequences, and the basis for guiding rapid interventions in response to such reports.

concluding section, the authors consider two paths for future research and development that might advance this field. A third issue raised during peer review of the manuscript will also be briefly addressed.

EMBRACE THE CLIMB TOWARD FDA APPROVAL

The authors of this circumspectives article concur with NIDA that patients with cocaine-use disorder, and public health in general, would benefit from more effective treatment including approved effective medications (NIDA, 2014b; O'Brien, 2011). Agonist medications are strong candidates for meeting this need, and some candidate agonist medications (eg, amphetamine, lisdexamfetamine, and phendimetrazine) already enjoy FDA approval for other indications that include treatment of attention deficit hyperactivity disorder, narcolepsy, and obesity. In this context, amphetamine-like drugs are already prescribed millions of times each year to a broad patient population of both children and adults (IMS Institute for Healthcare Informatics, 2014; Lin et al, 2005). Nonetheless, treatment of cocaine-use disorder would be a new indication for these drugs that would produce a modest increase in both the number of annual prescriptions and the segments of population to which the drug(s) might be prescribed. For example, the most recent data from SAMSHA indicated that cocaine was listed as the primary substance of abuse by 143 827 patients admitted for drug-abuse treatment in 2011, and most of these were more than 30 years old (SAMHSA, 2014b). Approval of existing amphetamine-like drugs for treatment of cocaine-use disorder in this population would require new FDA review, and the authors agree that existing data, while encouraging as proof of concept, are not yet sufficient to meet the demands of the FDA review process. Consequently, one path for future research would be to complement ongoing proof-of-concept testing with efforts to win FDA approval for the use of specific formulations of specific drugs for treatment of cocaine-use disorder in specific target populations.

Progress along this path will depend on a sequence of factors. First and foremost among these is the identification of a committed sponsor. The ultimate approval of buprenorphine products for treatment of opioid abuse depended on a sustained partnership between the pharma-

ceutical company that owned buprenorphine patents and a set of government agencies involved in drug-abuse control. The product of that partnership, Suboxone, is now among the best-selling drugs in the United States (IMS Institute for Healthcare Informatics, 2014). By contrast, no pharmaceutical companies are currently engaged in advancement of amphetamine-like products for treatment of cocaine abuse, and although NIDA has played a key role in supporting proof-of-concept testing, it lacks the resources to take a leadership role in seeking FDA approval. A second step will be the selection of a specific drug and formulation as a lead candidate for approval. For example, amphetamine is marketed in multiple forms that include immediate-release and extended-release formulations of either mixed isomers (eg, Adderall) or the active isomer only (dextroamphetamine, eg, Dexedrine), as well as the lysine-conjugated prodrug lisdexamfetamine (Vyvanse). It is not currently apparent whether one of these existing formulations, or some alternative formulation (or alternative drug), might serve as an optimal lead candidate for FDA approval. Third, it will be necessary to compile relevant safety data from clinical experience with the selected medication for its approved indications. Additional safety testing would ultimately be required in the target population of cocaine-abuse patients; however, data on the prevalence and severity of side effects in other populations (eg, patients with attention deficit hyperactivity disorder) could guide strategies for any new safety studies. Fourth, work could begin on preparation of the NDA, in part with the goal of identifying gaps that would require new studies for NDA completion. Finally, agonist medications in general, and amphetamine-like medications in particular, suffer politically from their own reputations as drugs of abuse. Advancement of agonist medications for treatment of cocaine abuse would benefit from identification of allies in congress to hold public hearings, assess needs and barriers in treatment development, and help pave the way for agonist therapy.

INVESTIGATE THE GENERALITY AND MECHANISMS OF AGONIST MEDICATION EFFECTS ON STIMULANT USE

Although existing research provides strong evidence for effectiveness of amphetamine maintenance to reduce cocaine

consumption, several outstanding questions remain, and research on these questions could contribute both to the development of improved medication candidates and to better understanding of basic processes in drug abuse. The authors of this circumspectives article agreed that two of those questions warrant discussion here. First, we have little information on the degree to which amphetamine-like medications that reduce cocaine consumption might also reduce consumption of other abused stimulants. Cocaine inhibits dopamine transporters, and some other drugs of abuse, such as methylenedioxypyrovalerone (MDPV), share this mechanism of action (Baumann et al, 2012b; Cameron et al, 2013). However, MDPV is both more potent and more selective than cocaine as a dopamine transporter inhibitor, and it is unknown whether amphetamine maintenance regimens that reduce cocaine consumption might also reduce consumption of MDPV or other abused dopamine transporter inhibitors. Notably, some other treatments have been found to differentially reduce abuse-related effects of cocaine vs MDPV (Bonano et al, 2014). The general class of abused stimulants also includes drugs such as amphetamine, methamphetamine, and emerging cathinone analogs that function as substrates at dopamine transporters to promote dopamine release (Baumann et al, 2012a; Cameron et al, 2013; Rothman et al, 2001). Recent clinical trials and a human laboratory study found that amphetamine maintenance failed to produce significant decreases in methamphetamine consumption (Galloway et al, 2011; Longo et al, 2010; Pike et al, 2014). These and related results have been interpreted to suggest that dopamine releasers such as amphetamine may be more effective to treat abuse of dopamine uptake inhibitors (eg, cocaine) than abuse of other dopamine releasers.

A second question that warrants further research is the mechanism that underlies amphetamine-induced decreases in cocaine use. One early hypothesis was that amphetamine maintenance might produce pharmacodynamic tolerance to its own effects and cross tolerance to the abuse-related effects of cocaine, eg, by downregulating dopamine transporters (Fleckenstein et al, 1999; Negus and Mello, 2003b). However, recent evidence does not support this hypothesis, and suggests instead that amphetamine maintenance may increase basal tone in dopaminergic signaling and thereby reduce abuse-related changes in dopamine signaling produced by cocaine (Bauer et al, 2014). A related question is whether mechanisms of the anti-cocaine effects of amphetamine maintenance can be dissociated from mechanisms of its side effects in general and its abuse-related effects in particular. In support of this possibility, a large body of research suggests that a subset of amphetamine effects, including its abuse-related effects, is mediated in part by increases in endogenous opioid release and activation of opioid receptors. For example, the opioid antagonists naloxone and/or naltrexone blunted abuse-related neurochemical and behavioral effects of amphetamine in microdialysis assays of dopamine release in the striatum (Hitzemann et al, 1982; Hooks et al, 1992) and in behavioral assays of intracranial self-stimulation in rats (Esposito et al, 1980; Holtzman, 1976), place conditioning in rats (Trujillo et al, 1991), and amphetamine self-administration in rhesus monkeys (Jimenez-Gomez et al, 2011). Naltrexone also reduced amphetamine subjective effects in non-dependent and amphetamine-dependent subjects, and reduced amphetamine abuse in a placebo-controlled double-blind clinical trial (Jayaram-Lindstrom et al, 2008a; Jayaram-Lindstrom et al, 2008b; Jayaram-Lindstrom et al, 2004). However, opioid antagonists do not block all amphetamine effects (van Kammen and Schulz, 1985; Winslow and Miczek, 1988; Wiskerke et al, 2011; Woolfolk and Holtzman, 1997), and it is unknown whether opioid mechanisms contribute to the anti-cocaine effects of amphetamine. Overall, research on these or other possible amphetamine mechanisms may suggest new strategies to dissociate the anti-cocaine effects of amphetamine from its undesirable effects.

METRICS OF THERAPEUTIC EFFICACY

Current preclinical and clinical trials of candidate medications for substance-use disorders assess medication efficacy by focusing on measures of drug-taking behavior and drug consumption (eg, rate of drug self-administration in animal studies and number of cocaine-positive urines in clinical trials). The FDA has also focused on measures of drug use as primary outcome measures in reviews of medications advanced as candidates to treat abuse of opioids, tobacco, and alcohol, as well as cocaine. For drugs other than tobacco, duration of participation in treatment ('treatment retention') is an additional important efficacy measure, and a variety of other measures may also be used in clinical trials and/or follow-up studies to assess potential treatment benefits, eg, criminal activity, job retention, and development of diseases such as HIV AIDS. These other measures may be important in justifying the benefits of treatment to payers and society at large, but they are not considered primary efficacy outcome measures on which to base drug approval. During peer review of this manuscript, it was noted that metrics of drug use are surrogate measures for clinically relevant outcomes that also include morbidity and mortality, and acceptance of agonist medications (or any other type of medication) for treatment of cocaine-use disorder will ultimately depend on evidence for reductions not only in cocaine use, but also in morbidity and mortality associated with cocaine use. The authors of this circumspectives article agree that morbidity and mortality are important concerns in treatment of drug abuse, and we agree that effective treatments should ultimately reduce their incidence. However, we do not recommend their inclusion as clinical endpoints for FDA approval for three reasons. First, the approval of all existing medications for substance-use disorders has been based primarily on efficacy to reduce measures of drug use, and such measures have proved valid as predictors of treatment outcome in clinical practice. Thus, it is our view that drug-use metrics have served as appropriate, accessible, and quantitative measures for evaluation of other drug-abuse treatments, and these criteria should also be appropriate for review of candidate medications for treatment of cocaine-use disorder. Second, the taxonomy of morbidity and mortality outcomes in cocaine-use disorder has not been clearly delineated or prioritized, and methods for quantifying those outcomes and incorporating them into preclinical and clinical research designs have not been adequately defined. This may be a topic for future research. Finally, and related

to the second point, mortality is an impractical measure in medication assessment, because its incidence is relatively low, and as a result, very large numbers of patients would need to be retained in treatment for long periods at a great expense to collect data sufficient for statistical analysis. We believe that any commercial sponsor would be unlikely to commit the resources and accept the high risks of uncertain outcome using such measures. Nonetheless, we agree that just as epidemiological studies have been useful in documenting the public health benefits of treatment for other substance-abuse disorders, so too should such studies be conducted to assess consequences of agonist therapies for cocaine abuse.

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