

Perspectives in Pharmacology

The Dopamine Transporter and Cocaine Medication Development: Drug Self-Administration in Nonhuman Primates

LEONARD L. HOWELL and KRISTIN M. WILCOX

Yerkes Regional Primate Research Center (L.L.H., K.M.W.), Department of Psychiatry and Behavioral Sciences (L.L.H.), and Department of Pharmacology (L.L.H.), Emory University, Atlanta, Georgia

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ABSTRACT

Despite intensive medication development efforts, no effective pharmacotherapy for cocaine abuse has demonstrated efficacy for long-term use. Given the obvious importance of the dopamine transporter in the addictive properties of cocaine, the development and use of compounds that target the dopamine transporter represents a reasonable approach for the pharmacological treatment of cocaine abuse. The therapeutic approach of replacement or substitute agonist medication has been successful, as shown with methadone maintenance for heroin dependence and nicotine replacement for tobacco use. A number of preclinical studies with dopamine transporter inhibitors provide evidence that substitute agonists may be used effectively to reduce cocaine use. Nonhuman primate models of drug self-administration provide a rigorous, systematic ap-

proach to characterize medication effectiveness in subjects with a documented history of drug use. Several cocaine analogs and other dopamine transporter inhibitors, including analogs of GBR 12909 and WIN 35,065-2, have been shown to reduce cocaine self-administration in nonhuman primates. A possible limitation to the use of selective dopamine transporter inhibitors as medications is their potential for abuse liability given their demonstrated reinforcing effects in nonhuman primates. However, limited reinforcing properties in the context of treatment programs may be advantageous, contributing to improved patient compliance and enhanced medication effectiveness. Moreover, pharmacokinetic properties that result in slow onset and long duration of action may enhance their effectiveness to reduce cocaine use while limiting their abuse liability.

Pharmacotherapy for Cocaine Addiction

Cocaine is widely recognized as one of the most addictive illicit drugs in use today, and abuse of cocaine in the United States remains a major public health problem. The 1997 National Household Survey on Drug Abuse estimated that 22.6 million Americans have used cocaine at least once in their lifetime, and that 1.5 million are current users [Substance Abuse and Mental Health Services Administration (SAMHSA), 1998]. In 1995, the estimated number of cocaine-related emergency episodes totaled over 142,000. Cocaine abuse continues at an epidemic level with significant costs to society, yet no uniformly effective pharmacotherapy for cocaine abuse has demonstrated efficacy for long-term use

(Carroll et al., 1999). The epidemic of stimulant abuse is exacerbated by the recent outbreak of methamphetamine use in West Coast cities and in western and southwestern communities. The SAMHSA Drug Abuse Warning Network reported that from 1991 to 1994, the number of methamphetamine-related visits to hospital emergency rooms more than tripled, from 4,887 to 17,397. Clearly, there is an urgent need to develop useful pharmacological treatments for stimulant abuse. Of the various types of medications being pursued, potent and selective dopamine transporter inhibitors represent a promising approach in drug development.

Rationale for Targeting the Dopamine Transporter

The dopamine transporter is a critical recognition site for cocaine and likely mediates its acute behavioral and reinforcing effects that contribute to significant abuse liability (Ritz et al., 1987; Kuhar et al., 1991). In vitro studies have dem-

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ABBREVIATIONS: RTI-113, 3 β -(4-chlorophenyl)tropane-2 β -carboxylic acid phenyl ester; PTT, 2 β -propanoyl-3 β -(4-tolyl)-tropane; GBR 12909, 1-(2-[bis(4-fluorophenyl)methoxy]ethyl)-4-(3-phenylpropyl)piperazine; PET, positron emission tomography.

onstrated that cocaine blocks the presynaptic uptake of the monoamines, dopamine, serotonin, and norepinephrine (Kuhar, 1993; Wilcox et al., 1999), but the behavioral effects of cocaine have been linked more closely to enhanced dopaminergic activity due to inhibition of dopamine uptake (Ritz et al., 1987; Woolverton and Johnson, 1992). Evidence to support this conclusion is derived from a variety of behavioral studies characterizing the acute effects of dopamine uptake inhibitors, direct agonists, and antagonists administered alone or in combination with cocaine. For example, preclinical studies have demonstrated a significant correlation between dopamine transporter occupancy and the psychomotor-stimulant (Cline et al., 1992; Kuhar, 1993) and reinforcing (Ritz et al., 1987; Bergman et al., 1989; Wilcox et al., 1999) effects of a variety of dopamine transporter inhibitors from distinct structural classes. Importantly, recent neuroimaging studies in human cocaine users have found a significant correlation between dopamine transporter occupancy and the subjective high reported following administration of cocaine (Volkow et al., 1997) or methylphenidate (Volkow et al., 1999). Collectively, the results obtained in behavioral studies provide compelling evidence that dopamine plays a major role in the neuropharmacology and addictive properties of cocaine.

Given the obvious importance of the dopamine transporter in the addictive properties of cocaine, the development and use of compounds that target the dopamine transporter would seem to be a reasonable approach for the pharmacological treatment of cocaine abuse. The therapeutic approach of replacement or substitute agonist medication has been successful, as shown with methadone maintenance for heroin dependence and nicotine replacement for tobacco use. These successes, combined with significant advances in the understanding of the neurobiological basis of cocaine dependence, support efforts to discover a similar type of medication for cocaine abuse. An effective substitute pharmacotherapy would have the immediate advantage of attracting the drug user to a treatment center and facilitate entry into a program where long-term abstinence is the final goal (Carroll et al., 1999). A number of preclinical studies with dopamine transporter inhibitors provide evidence that substitute agonists may be used effectively to reduce cocaine use (for reviews see Witkin, 1994; Rothman and Glowa, 1995; Mello and Negus, 1996).

Nonhuman Primate Models of Drug Self-Administration

Drug self-administration procedures in animals have proven to be valid and reliable models for evaluating the abuse liability of drugs in humans. Nonhuman primate models of drug self-administration have provided a rigorous, systematic approach to characterize the reinforcing effects of psychoactive drugs (Howell and Wilcox, 2001). The longevity of nonhuman primates has enabled long-term studies to be conducted and repeated-measures designs to be used. A single venous catheter can be maintained readily for over a year, and multiple implants permit the conduct of self-administration experiments for several years in individual subjects. Long-term studies with repeated measures are well suited for comprehensive drug-interaction experiments. Moreover, the

use of nonhuman subjects that are anatomically and physiologically similar to humans have allowed for the development of a clear and clinically relevant characterization of medication effectiveness in subjects with a documented history of drug use under well controlled laboratory conditions. The problems of polydrug use and lifestyle characteristics that are major concerns in human studies are eliminated.

Research efforts using nonhuman primate models of drug self-administration have focused primarily on the identification of neurochemical mechanisms that underlie drug reinforcement, and on the development of pharmacotherapies to treat drug abuse. Preclinical evaluations of pharmacotherapies require the establishment of stable baseline patterns of drug self-administration prior to drug interaction studies. Subsequently, the treatment medication is administered as a pretreatment before the conduct of self-administration sessions. It is critical to study several doses of the treatment medication to determine an effective dose range and a maximally effective dose that lacks overt behavioral toxicity. The effects of the treatment medication typically are evaluated first in combination with a dose of the self-administered drug that maintains high rates of self-administration. However, multiple doses should be characterized for the self-administered drug because pretreatment effects can differ depending on the unit dose of the drug self-administered. Medications that shift the dose-effect curve downward and decrease self-administration over a broad range of unit doses are most likely to have therapeutic utility. Medications that shift the dose-effect curve to the right and simply alter the potency of the self-administered drug may prove to be ineffective at higher unit doses. Studies should include repeated daily exposure to the medication to characterize peak effectiveness and to document continued effectiveness over multiple sessions.

The primary treatment outcome measures in drug self-administration studies are 1) rate of responding and 2) the number of drug injections delivered per session. Both measures are influenced by the schedule of reinforcement and drug dose. Moreover, most self-administered drugs have direct effects on rate of responding that may be distinct from their reinforcing effects. For example, cocaine injections may increase rate of responding early in the session but suppress behavior later in the session as total drug intake accumulates. Another important consideration in evaluating medication effectiveness is the selectivity of effects on drug self-administration. If the drug pretreatment decreases drug self-administration at lower doses or to a greater extent than behavior maintained by a nondrug reinforcer such as food, the outcome is indicative of selective interactions with the reinforcing properties of the self-administered drug. In contrast, a general sedative effect will likely suppress drug- and food-maintained responding to a comparable extent. Lastly, the reinforcing properties of the medication are evaluated by substituting a range of doses of the medication for the self-administered drug. Because reinforcing effects in preclinical studies have been correlated with abuse liability in humans, the evaluation of medication effectiveness in maintaining self-administration over a range of experimental conditions is an important consideration.

Dopamine Transporter Inhibitors and Cocaine Self-Administration

A variety of preclinical studies in nonhuman primates provide evidence that selective inhibitors of dopamine uptake may be useful pharmacotherapies in the treatment of cocaine abuse. Several cocaine analogs and other dopamine transporter inhibitors, including analogs of GBR 12909 and WIN 35,065-2, have been developed and characterized for their ability to reduce cocaine self-administration. Perhaps the largest class of compounds studied is the 3-phenyltropane analogs (Carroll et al., 1999). The phenyltropane analog 3 β -(4-chlorophenyl)tropane-2 β -carboxylic acid phenyl ester (RTI-113) effectively decreased cocaine self-administration in squirrel monkeys trained under a second-order schedule of i.v. cocaine delivery (Howell et al., 2000). Moreover, RTI-113 maintained its effectiveness when the unit dose of cocaine was increased from 0.1 to 0.3 mg/kg/injection, indicating that the ability of RTI-113 to suppress cocaine self-administration could not be surmounted by a higher dose of cocaine. However, the same dose of RTI-113 caused a general disruption of operant behavior maintained by a comparable schedule of stimulus-shock termination, thereby demonstrating that behaviorally active doses of RTI-113 were required to decrease cocaine-maintained behavior. Similar results have been obtained with the cocaine analog 2 β -propanoyl-3 β -(4-tolyl)-tropane (PTT) in rhesus monkeys trained under a fixed-interval schedule of i.v. cocaine delivery (Nader et al., 1997). Presession administration of PTT decreased response rates and total session intake at multiple unit doses of cocaine (0.03 and 0.1 mg/kg/injection).

The effectiveness of selective dopamine transporter inhibitors to decrease cocaine self-administration extends to phenylpiperazine derivatives. 1-(2-[bis(4-fluorophenyl)-methoxy]ethyl)-4-(3-phenylpropyl)piperazine (GBR 12909) dose dependently decreased cocaine self-administration in rhesus monkeys trained under multiple fixed-ratio schedules of i.v. cocaine and food delivery (Glowa et al., 1995a). Although GBR 12909 decreased rates of responding maintained by cocaine and food, large decreases in cocaine-maintained responding could be obtained at doses of GBR 12909 that had little effect on food-maintained responding. Hence, there was evidence for a selective decrease in cocaine-maintained responding at a low unit dose of cocaine (0.01 mg/kg/injection). However, the selectivity was not evident at a higher unit dose of cocaine (0.056 mg/kg/injection), suggesting that the effectiveness of GBR 12909 to decrease cocaine self-administration is sensitive to the unit dose of cocaine used to maintain behavior. When GBR 12909 was administered chronically as a decanoate derivative, selective reductions in cocaine self-administration were sustained over a four-week period (Glowa et al., 1996). The same doses of GBR 12909 found to decrease cocaine self-administration in rhesus monkeys were subsequently tested in baboons to determine the proportional occupancy of dopamine transporters *in vivo* (Villemagne et al., 1999). Positron emission tomography (PET) with [¹¹C]WIN 35,428 was used to quantify dopamine transporter occupancy by GBR 12909. The results obtained indicated that GBR 12909 must occupy a substantial fraction (>50%) of dopamine transporters to decrease cocaine self-administration in nonhuman primates.

Not all high-affinity dopamine transporter inhibitors ex-

hibit a profile considered favorable for a substitute agonist medication. Clearly, pharmacological properties other than dopamine transporter inhibition, as well as pharmacokinetic considerations, can influence the effectiveness of a compound to decrease cocaine self-administration. The phenylpiperazine, GBR 12935, the long-acting cocaine analog, (-)-2- β -carbomethoxy-3- β -(4-fluorophenyl)tropane, and *d*-amphetamine all failed to produce selective decreases in cocaine self-administration in rhesus monkeys trained under multiple fixed-ratio schedules of i.v. cocaine and food delivery (Glowa et al., 1995b; Glowa and Wojnicki, 1996). Similarly, continuous i.v. infusions of the dopamine transporter inhibitor, mazindol, had effects on food-maintained responding at the same doses and with the same time course as cocaine-maintained responding in rhesus monkeys (Kleven and Woolverton, 1993). While selectivity of effects on drug-maintained behavior is a desirable outcome, the nature of the alternative reinforcer and the behavior engendered are important considerations. For example, the use of food-maintained behavior to access the selectivity of stimulant pretreatments could bias against a positive outcome due to their anorexic effects. Clearly, the types of side effects that are viewed as tolerable should be evaluated in the context of medication effectiveness in reducing drug use.

Abuse Liability of Dopamine Transporter Inhibitors

A possible limitation to the use of selective dopamine transporter inhibitors as medications for cocaine abuse is their potential for abuse liability given their demonstrated reinforcing effects in nonhuman primates. The phenyltropane, RTI-113, was reliably self-administered by squirrel monkeys when substituted in subjects trained to self-administer cocaine. There was considerable between-subject variability, but RTI-113 maintained rates of responding for the group comparable with those maintained by cocaine (Howell et al., 2000). Similarly, the phenylpiperazine derivative, GBR 12909, also maintained rates of i.v. self-administration comparable with those of cocaine in squirrel monkeys (Bergman et al., 1989; Howell and Byrd, 1991; Howell et al., 1997). These findings are consistent with other reports that bupropion, methylphenidate, and nomifensine were self-administered by rhesus monkeys (Johanson and Schuster, 1975; Winger and Woods, 1985). Also, local anesthetics that bind to dopamine transporters and inhibit dopamine uptake were self-administered by rhesus monkeys, and their reinforcing potency was related to their affinity at dopamine transporters (Wilcox et al., 1999) and to their effectiveness in inhibiting dopamine uptake (Wilcox et al., 2000). Hence, dopamine transporter inhibition is related to the reinforcing effects of compounds from very diverse structural classes. However, demonstration of reinforcing effects in nonhuman primate models does not necessarily imply high abuse liability in the context of clinical treatment programs. It is critical to consider the pattern of self-administration maintained by the medication and the range of conditions under which self-administration can be sustained. Limited reinforcing properties may be advantageous and contribute to improved patient compliance and enhanced medication effectiveness. The goal of pharmacotherapy is to enhance retention in treatment programs and reduce illicit drug use. Reinforcing properties

Therapeutics and Transporter Occupancy

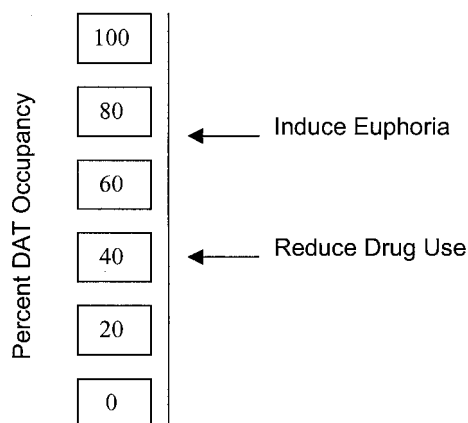


Fig. 1. Possible therapeutic and euphoric effects of a hypothetical dopamine transporter inhibitor at different levels of dopamine transporter occupancy.

that engender reliable self-administration of the medication may contribute to these criteria for successful treatment.

Figure 1 illustrates possible therapeutic and euphoric effects of a hypothetical dopamine transporter inhibitor at different levels of dopamine transporter occupancy. A critical assumption of the model is that reductions in drug use can be obtained at lower levels of dopamine transporter occupancy compared with those required to induce euphoria. Hence, a therapeutic effect may be achieved without significant abuse liability. In nonhuman primates, this outcome could be reflected in drug doses that effectively reduce cocaine self-administration without maintaining robust self-administration under the same range of conditions established for cocaine. PET neuroimaging studies have used the selective dopamine transporter ligand, 2 β -carbomethoxy-3 β -(4-chlorophenyl)-8-(2-fluoroethyl)nortropine ([¹⁸F]FECNT), to determine dopamine transporter occupancy by cocaine in rhesus monkeys with a history of cocaine self-administration (Table 1). Note that doses of cocaine that are reliably self-administered occupied 53 to 87% of dopamine transporters based on this analysis. It remains to be determined whether selective dopamine transporter inhibitors will exhibit the profile of occupancy and behavioral effects depicted in Fig. 1.

As noted previously, pharmacokinetic properties can influence the profile of behavioral effects. Structural modifications that limit absorption and entry into the brain, resulting in slower onset and longer duration of action, could effectively reduce the abuse liability of candidate

TABLE 1
Percentage of dopamine transporter occupancy determined with PET following i.v. cocaine administration

Subject	Cocaine Dose	
	0.1 mg/kg	1.0 mg/kg
RMk-3	53.0	92.1
RLm-1	55.8	95.5
RL1-4	44.2	84.0
RLk-4	52.7	83.6
RSu-3	59.1	88.0
Avg. \pm S.D.	53 \pm 5	87 \pm 5

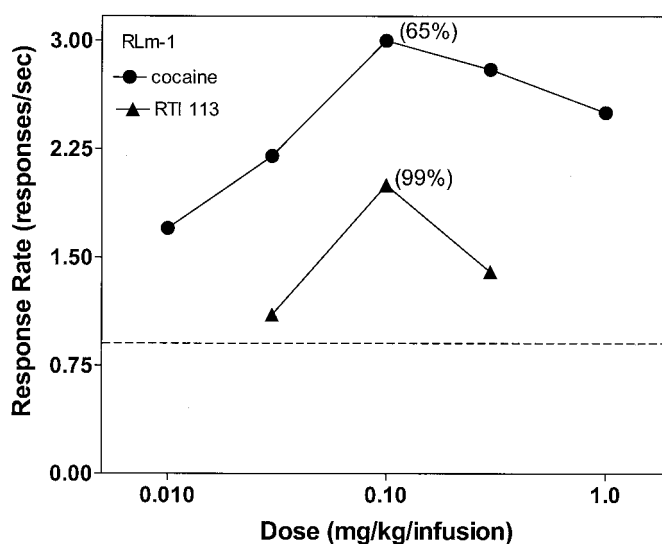


Fig. 2. Response rate (responses/s) maintained by cocaine and RTI-113 as a function of drug dose under a second-order fixed-interval (600-s), fixed-ratio (20) response schedule of i.v. drug administration in rhesus monkey RLm-1. Dashed line, the upper limit of responding during saline extinction conditions. Each data point is the mean of the last five sessions in a condition.

compounds. Although RTI-113 has a fairly rapid onset of action that cannot be distinguished from cocaine, it has a longer duration of action that may influence the pattern of self-administration (Howell et al., 2000). Figure 2 compares response rates maintained by cocaine and RTI-113 over a range of drug doses in a rhesus monkey. Note that peak rates of responding were much greater for cocaine compared with RTI-113, even though dopamine transporter occupancy was less for cocaine (65%) compared with RTI-113 (99%). Clearly, reinforcing effectiveness and the pattern of drug self-administration are not determined exclusively by pharmacodynamic properties related to transporter occupancy under steady-state conditions.

Similarly, the selective dopamine uptake inhibitor, PTT, has a slower onset and much longer duration of action than cocaine, and it reliably decreases cocaine self-administration without maintaining self-administration behavior under fixed-interval schedules in nonhuman primates (Nader et al., 1997). Although PTT maintains response rates significantly higher than those maintained by vehicle under fixed-ratio schedules, response rates are significantly lower than those maintained by cocaine (Birmingham et al., 1998; Lile et al., 2000). Hence, PTT maintains self-administration, but it exhibits reinforcing effects over a narrower range of experimental conditions that vary drug history, schedule of reinforcement, and frequency of drug access. In addition, several benztrapine analogs have been shown to maintain low rates of responding in rhesus monkeys trained under a fixed-ratio schedule of i.v. drug delivery, even though the compounds have higher affinities than cocaine at the dopamine transporter (Woolverton et al., 2000). It is unclear whether the limited reinforcing effects of benztrapines are due to pharmacokinetic properties or to their complex binding profile at other monoamine transporters and muscarinic receptors.

Serotonin and Norepinephrine Transporter Inhibitors

Cocaine is nonselective in its inhibition of monoamine uptake and has high affinity at serotonin and norepinephrine transporters. In fact, there is a negative correlation between the potencies of several cocaine analogs in self-administration studies and their binding potency to serotonin uptake sites (Ritz et al., 1987). Moreover, studies in nonhuman primates demonstrate that selective serotonin uptake inhibitors can attenuate the behavioral-stimulant and reinforcing effects of cocaine and related psychomotor stimulants (Kleven and Woolverton, 1993; Howell and Byrd, 1995; Howell et al., 1997) with no evidence of abuse liability (Vanover et al., 1992; Howell and Byrd, 1995). Norepinephrine transporter inhibitors appear less promising and typically fail to reduce cocaine self-administration in nonhuman primates. Pretreatment with desipramine in rhesus monkeys trained under a second-order schedule of i.v. cocaine delivery had inconsistent effects and actually increased cocaine self-administration in some animals (Mello et al., 1990). In addition, food-maintained behavior was affected by pretreatment doses that influenced drug self-administration, demonstrating a lack of selectivity. In another study, pretreatment with desipramine in rhesus monkeys trained under multiple fixed-ratio schedules of i.v. cocaine and food delivery had no effect on cocaine self-administration (Kleven and Woolverton, 1990). Indatraline is an example of a nonselective monoamine transporter inhibitor with similar nanomolar potencies at dopamine, serotonin, and norepinephrine transporters. Pretreatment with indatraline in rhesus monkeys trained under alternating daily sessions of cocaine and food availability produced dose-dependent decreases in cocaine self-administration over a broad range of cocaine doses (Negus et al., 1999). Moreover, reductions in cocaine self-administration were sustained during 7 consecutive days of indatraline pretreatment. When substituted for cocaine in self-administration sessions, indatraline maintained lower rates of responding compared with cocaine. Unfortunately, indatraline had undesirable side effects, including behavioral stereotypies and trends toward weight loss that may limit its clinical utility.

Clinical Relevance for Medications Development

Recent efforts to develop dopamine transporter inhibitors as pharmacotherapies for cocaine abuse are based on sound theoretical considerations and promising empirical data derived from preclinical research. Nonhuman primate models of drug self-administration simulate important aspects of drug use in humans and provide a clinically relevant paradigm to evaluate medication effectiveness. A variety of drugs that inhibit dopamine transporter function can reliably suppress cocaine self-administration over a broad range of experimental conditions. Although human studies using dopaminergic drugs have failed to yield encouraging results (Mendelson and Mello, 1996), clinical trials have not been conducted with selective dopamine transporter inhibitors. Accordingly, studies should continue to characterize the therapeutic efficacy and safety of these compounds to identify lead candidates for evaluation in clinical trials. While pre-

clinical investigations have focused on measures of transporter binding and occupancy, there is a clear absence of information relating behavioral endpoints predictive of therapeutic efficacy to functional measures of dopamine transporter inhibition.

Several pharmacological properties of dopamine transporter inhibitors may be desirable for clinical effectiveness. Compounds that bind with high affinity to the dopamine transporter and dissociate slowly could function as noncompetitive inhibitors of cocaine binding, thereby reducing the effectiveness of cocaine (Rothman and Glowa, 1995). Moreover, chronic, steady-state elevations in extracellular dopamine induced by the medication could ostensibly normalize a dysfunctional dopaminergic system and suppress the negative symptoms associated with cocaine abstinence. The concept of substitute agonist pharmacotherapy implies that the medication will exhibit some cocaine-like properties at a neurochemical and behavioral level. The majority of selective dopamine transporter inhibitors identified exhibit psychomotor-stimulant effects and are self-administered in preclinical studies. If the latter effects are robust and evident over a broad range of experimental conditions, they may prove to be undesirable properties of the medication. However, a pharmacokinetic profile of slow onset and long duration of action may limit undesirable behavioral effects and reduce the abuse liability of the candidate medication.

Summary

There is a clear need to develop useful pharmacological treatments for cocaine abuse. Of the various types of medications being pursued, potent and selective dopamine transporter inhibitors represent a promising approach in drug development. A variety of preclinical studies in nonhuman primate models of drug self-administration provide evidence that selective dopamine transporter inhibitors can effectively reduce cocaine use. A possible limitation to their use as medications for cocaine addiction is their potential for abuse liability given their demonstrated reinforcing effects in nonhuman primates. However, limited reinforcing properties may be advantageous and contribute to improved patient compliance in treatment programs. Moreover, pharmacokinetic properties that result in slow onset and long duration of action may enhance their effectiveness to reduce cocaine use while limiting their abuse liability.

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Address correspondence to: Dr. Leonard L. Howell, Yerkes Regional Primate Research Center, Emory University, Atlanta, GA 30322. E-mail: leonard@rmy.emory.edu
