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# Controversies in translational research:

## Drug self-administration

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## Abstract

**Rationale—**Laboratory animal and human models of drug self-administration are used to evaluate potential pharmacotherapies for drug abuse, yet the utility of these models in predicting clinically useful medications is variable.

**Objective—**The objective of this study was to track how antagonist, agonist, and partial agonist medication approaches influence heroin and cocaine self-administration by rodents, non-human primates, and humans and to compare these results to clinical outcomes.

**Results—**Across species, heroin self-administration was decreased by all three medication approaches, paralleling their demonstrated clinical utility. The heroin data emphasize the importance of assessing a medication's abuse liability preclinically to predict medication abuse and compliance and of considering subject characteristics (e.g., opioid dependence) when interpreting medication effects. For cocaine, the effects of ecopipam, modafinil, and aripiprazole were consistent in the laboratory and clinic, provided that the medications were administered repeatedly before self-administration sessions. Modafinil attenuated cocaine's reinforcing effects in the human laboratory and improved treatment outcome, while ecopipam and aripiprazole increased the reinforcing effects of cocaine and do not appear promising in the clinic.

**Conclusions—**The self-administration model has reliably identified medications to treat opioid dependence, and the recent data with modafinil suggest that the human laboratory model also identifies medications to treat cocaine dependence. There have been numerous false positives when subjective effects are the primary outcome measure, but not when self-administration is the outcome. Factors relevant to the predictive validity of self-administration procedures include medication maintenance and the concurrent assessment of a range of behaviors to determine abuse liability and the specificity of effect.

### Keywords

Cocaine; Opioid; Naloxone; Dopamine receptor; Drug abuse; Model; Monkey; Human; Reinforcement

Laboratory testing of potential pharmacotherapies for drug abuse is an essential component of medication development. Although well-designed clinical trials are the standard by which the efficacy of a new medication is assessed, clinical trials test the effects of a potential treatment


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medication on a broad sample of patients, which is both costly and potentially risky. Before exposing a large number of treatment seekers to a medication, there needs to be both a strong scientific rationale for combining the medication with a drug of abuse as well as a demonstration that the co-administration of the medication and the abused drug is safe and selectively modifies the behavior of interest: drug taking.

Models of drug self-administration in rodents, non-human primates, and humans have been used to evaluate the effects of candidate medications for the treatment of drug dependence. The self-administration model provides meaningful behavioral data on the safety and efficacy of potential treatment medications in a relatively small number of individuals under carefully controlled conditions. It has been hypothesized that medications that selectively decrease self-administration of drugs in the laboratory would be useful in decreasing drug use in the clinic. Is this the case?

Many of the issues related to the validity of preclinical self-administration models have been thoroughly described (Mello and Negus 1996). The objective of this review was to focus on two drugs of abuse, heroin and cocaine, and to track how select medications made the journey from rodent, non-human primate, and human self-administration studies to the clinic. The over-arching question is whether medication effects on heroin and cocaine self-administration (human and non-human models) predict behavior in individuals seeking treatment for their drug use. In cases where there is inconsistency, we will address the issues we believe are important in improving the predictive validity of self-administration models in medications development. Promising targets and procedural approaches to improve the predictive validity of self-administration procedures for medications development will also be discussed.

## Overview of self-administration procedures

### Rodents and non-human primates

The origin of the drug self-administration technique can be traced back to studies of morphine dependence in chimpanzees by Spragg (1940), while the widespread use of the procedure stems from the development of reliable, automated methods for intravenous (i.v.) drug self-administration in rats and monkeys in the 1960s (e.g., Weeks 1962; Thompson and Schuster 1964; Pickens 1968; Woods and Schuster 1968; Deneau et al. 1969). The acceptance of animal drug self-administration procedures as a viable research tool derives not only from the face validity of the technique but, even more important, from the finding that animals will reliably self-administer most drugs that are abused by humans (e.g., Schuster and Johanson 1974; Johanson and Balster 1978). The predictive validity of drug self-administration techniques in animals for identifying drugs with high abuse liability in people (Brady et al. 1987; Balster 1991; Lile and Nader 2003) has made the procedure virtually indispensable for the screening of investigational drugs for abuse potential and has promoted the idea that these techniques are also useful for identifying effective pharmacotherapies to treat drug addiction. In addition, drug self-administration techniques in animals remain among the most relevant procedures for investigating neurobiological mechanisms underlying the process of drug reinforcement.

Drugs can be self-administered by various routes of administration, but in the case of cocaine and heroin, the majority of studies in animals have been conducted using the i.v. route in which drug injections are delivered to the subject contingent on performance of a specified response such as pressing a lever or operating a key. The contingencies that determine when and how many responses are required to produce an injection are determined by the schedule of reinforcement, which are simply those rules that govern the sequential and temporal relations between responses and reinforcers. A formal classification of schedules of reinforcement is often made on the basis of whether an injection follows a specified number of responses (ratio schedules) or follows a response after a specified period of time has elapsed (interval

schedules). The majority of studies involving cocaine or heroin self-administration have employed simple fixed-ratio (FR) schedules, with a substantial minority of studies using progressive-ratio (see reviews by Richardson and Roberts 1996; Stafford et al. 1998), second-order (see reviews by Everitt and Robbins 2000; Schindler et al. 2002), or fixed-interval schedules (see reviews by Spealman and Goldberg 1978; Corrigall and Coen 1989). Each type of schedule engenders its own characteristic temporal pattern and rate of responding, which are remarkably reproducible across species, type of operant conditioning task, and type of reinforcer (e.g., food, drug, etc.). These characteristic schedule-controlled performances can provide a meaningful way to compare behavior maintained by drugs and other types of reinforcers, but can impose limitations on direct comparisons across experiments using different schedules of drug self-administration. In general, such limitations are minimally restrictive in studies focusing on the reinforcing effects of drugs with high abuse liability, but may play a critical role in testing the effects of a potential medication to treat cocaine or heroin addiction. For example, a candidate medication with antagonist properties might increase drug self-administration under a single-response FR schedule but decrease self-administration under a schedule with greater response demands or intermittency (e.g., progressive ratio or second-order schedule).

Over the past several years, researchers have increasingly modified drug self-administration procedures to bring them more in line with the conditions that are encountered by drug-dependent individuals. These modifications may include provisions for “binge” patterns of cocaine self-administration or more widely spaced patterns of heroin self-administration and pairing environmental stimuli such as lights or sounds that are explicitly associated with drug injection or drug availability to mimic the myriad of environmental cues associated with cocaine or heroin drug purchase, preparation, and use. In addition, studies with laboratory animals may include alternative sources of reinforcement, such as food, that are in effect either concurrently or sequentially with the opportunity to self-administer a drug in order to mimic the non-drug choices available to drug-dependent individuals.

Evaluated over a sufficiently wide range of doses, drug self-administration data in animal studies are frequently characterized by an inverted U-shaped function relating the drug dose and an appropriate measure of behavior such as response rate or number of self-administered injections. The characteristic inverted U-shaped dose-response curves for cocaine, heroin, and other drugs typically reflect an interaction between the reinforcing effects of the drug and its other direct effects on behavior, which tend to emerge over successive injections of high doses. Consequently, the ascending portion of the inverted U-shaped curve may provide the most unambiguous information regarding a drug’s reinforcing effects, and it is this portion of the dose-response curve that is typically studied in the human laboratory where safety concerns override the testing of potentially dangerous doses. As biphasic dose-response curves do not always lend themselves well to simple analysis, some researchers circumvent the problem by limiting drug intake to only a single injection per day, imposing sufficiently long inter-trial intervals to permit drug washout and focusing on dependent variables other than response rate, such as the proportion of responses allocated to the “drug” lever in a choice procedure involving drug and non-drug alternatives or “break point” in the case of progressive-ratio schedules (Griffiths et al. 1976; Woolverton and Balster 1981; Stafford et al. 1998;Negus 2006).

The basic design for preclinical evaluation of a potential pharmacotherapy for cocaine or heroin abuse in animals is similar to designs used in human laboratory studies. In a typical animal study, once stable drug self-administration is established, test sessions are conducted by administering a candidate pharmacotherapy or its vehicle as a pretreatment before the self-administration session, and the effect of the medication relative to vehicle is measured. Studies of this type typically test an appropriate range of doses of both the candidate medication and the self-administered drug to determine how the shape and position of the self-administration

dose-response curve are altered as a result of drug pretreatment. Depending on the outcome, the candidate medication also may be evaluated for its own ability to maintain self-administration when substituted for cocaine or heroin. Collectively, such studies can identify drugs that alter cocaine or heroin self-administration in a manner suggestive of potential clinical utility, as well as information concerning the drug's potential for patient acceptability and/or abuse.

In practice, drug self-administration studies focusing on medication development in animals are often paired with corresponding studies involving non-drug reinforcers, such as food, to determine the specificity with which a candidate medication affects drug-reinforced behavior. Additional studies using drug discrimination procedures and other quantitative behavioral assessments also are frequently conducted in parallel with drug self-administration studies to provide relevant information about how the candidate medication may alter the interoceptive effects of the self-administered drug and about potential side effects. Such supplemental studies correspond roughly with the subjective effects and drug rating scales used to augment drug self-administration data in human laboratory studies.

## Humans

*Heroin* As in laboratory animal studies, human models of drug self-administration utilize operant conditioning procedures to provide objective and quantitative measures of drug-reinforced behavior (Mello et al. 1981a). Human laboratory models have characterized intravenous (Altman et al. 1976; Mello and Mendelson 1980; Mello et al. 1981a, 1982) and intranasal (Comer et al. 1997) routes of heroin self-administration. In some procedures, self-administration is assessed in individuals who are currently opioid-dependent. Comer et al. (1997, 1999, 2001), for example, maintained volunteers on oral morphine, to avoid the onset of opioid withdrawal while determining the reinforcing effects of heroin using a progressive-ratio schedule. Oral morphine administration, which produces minimal subjective response in dependent individuals, removes the confound of opioid withdrawal from the determination of heroin's reinforcing effects. An alternative approach is to have heroin-dependent volunteers undergo withdrawal before self-administration sessions. This detoxification is necessary, for example, when testing the effects of opioid antagonists on heroin self-administration to avoid precipitating withdrawal (e.g., Mello et al. 1981a).

Unlike cocaine, heroin is typically not used in a binge pattern, but has an inter-dose interval of hours rather than minutes. Thus, in some procedures, heroin may be self-administered in a bolus at the end of an experimental session (e.g., Comer et al. 1997) in which volunteers respond under a progressive-ratio schedule for a dose of heroin and for vouchers exchangeable for money. Participants receive whatever combination of heroin and money they had earned after the session is completed. In other procedures, participants have self-administered single doses of heroin at 6-h intervals. During the 6-h interval, participants have the option to respond on tasks to earn either money or heroin (Mello et al. 1981a). These studies demonstrate that heroin self-administration is dose-dependent, with both i.v. and intranasal heroin producing comparable break point values (Comer et al. 1999). Further, choice for heroin decreases as the value of the alternative reinforcer increases (Comer et al. 1998).

*Cocaine* In the natural ecology, cocaine is primarily used in a binge pattern where doses are repeatedly administered with short inter-dose intervals. Thus, in the laboratory, cocaine-dependent volunteers are typically given the opportunity to self-administer a range of cocaine doses repeatedly over several hours under careful medical observation. The opportunity to respond to receive doses of cocaine may occur at 10- to 40-min intervals depending on the route of administration (Foltin and Fischman 1996; Hatsukami et al. 1994; Dudish-Poulsen and Hatsukami 1997; Haney et al. 2001; Foltin and Haney 2004; Donny et al. 2003, 2004; Walsh et al. 2001). This procedure, along with concurrent measurement of subjective effects

and physiological markers, provides dose- and time-dependent data on i.v., smoked and intranasal cocaine self-administration, cocaine craving, subjective-effects ratings, and cardiovascular effects. Smoked cocaine has the fastest rate of onset, followed by intravenous, intranasal, and oral routes (see Bigelow and Walsh 1998). Smoked cocaine also produces greater increases in ratings of "high" and "liking" than i.v. cocaine despite equivalent cocaine plasma levels and is preferentially self-administered when participants are given a choice between smoked versus i.v. cocaine (Foltin and Fischman 1991, 1992).

In many procedures, volunteers are instructed to "sample" the dose of cocaine that is available during the session and are subsequently given repeated opportunities to choose between that dose and an alternative reinforcer, such as a voucher worth $5.00. This sampled dose may function as a "prime" to increase the likelihood of further cocaine use (Spealman et al. 1999). Once cocaine use is initiated, the probability is high that more cocaine will be self-administered shortly thereafter even when the alternative to using cocaine is of considerable value, e.g., monetary reinforcers worth four times more than the street value of the dose of cocaine (Walsh et al. 2001; Donny et al. 2003, 2004).

By assessing both cocaine self-administration and a range of subjective-effects rating scales, the model can be used to determine whether a candidate medication shifts choice away from cocaine to alternative, non-drug reinforcers, and if so, by what potential mechanism. That is, a medication that decreases cocaine self-administration may do so by specifically altering cocaine's reinforcing effects or by nonspecifically sedating the volunteers or making them feel ill, decreasing cocaine craving, or by altering the perception of cocaine's effects (e.g., increasing anxiety and decreasing a perceived "good drug effect").

## Opioid self-administration and medication effects

### Antagonist approach: naltrexone

**Rodents and non-human primates—**The relatively early development of safe and effective mu opioid antagonists, such as naloxone and naltrexone (Blumberg and Dayton 1974), prompted wide speculation that this class of drugs might be used successfully to treat the problem of heroin addiction. This speculation was supported by the consistent finding that naloxone and naltrexone effectively reduced opiate self-administration in rodents (Weeks and Collins 1976; Ettenberg et al. 1982; Koob et al. 1984) and non-human primates (Griffiths et al. 1976; Harrigan and Downs 1978). Follow-up studies involving comprehensive dose-response analyses, the availability of alternative reinforcers, and chronic treatment regimens have continued to offer compelling evidence that naloxone and naltrexone induce a selective antagonism of heroin's reinforcing effects (Bertalmio and Woods 1989; Rowlett et al. 1998; Negus 2006). Doses of the antagonists typically used in these studies produced few adverse effects in non-dependent subjects but were sufficient to precipitate withdrawal signs in animals rendered physically dependent to mu opioid agonists.

**Human laboratory—**Naltrexone (50, 75 mg/day p.o.) has also been shown to suppress heroin self-administration in detoxified heroin-dependent volunteers. Specifically, under placebo maintenance conditions, research volunteers self-administered 57.5-100% of the total heroin available, whereas under naltrexone maintenance, participants took only 2.0-7.5% of the total heroin available (Meyer and Mirin 1979; Mello et al. 1981b). More recently, depot formulations of naltrexone have been developed as an alternative to the oral route of administration. In the laboratory, depot naltrexone (384 mg s.c.) has been shown to antagonize the reinforcing and subjective effects of heroin (up to 25 mg i.v.) for 4-5 weeks (Comer et al. 2002b; Sullivan et al. 2006).

**Clinical trial—**Naltrexone safely and effectively blocks the effects of heroin when used clinically, consistent with the laboratory data in humans and laboratory animals. Yet, oral naltrexone is not an effective treatment medication because of poor patient compliance (O'Brien et al. 1975; Schecter 1980; Capone et al. 1986). Clinical trials with naltrexone have demonstrated efficacy in only a subset of highly motivated patients, such as physicians who will lose their medicallicense if they return to opioid use. The majority of patients discontinue naltrexone use within days or weeks. It appears that the daily decision to either take a highly potent reinforcer (heroin) or to take a medication with no reinforcing effects to block the effects of heroin (naltrex-one) eventually results in a high dropout rate and a return to heroin use (Kleber 1985).

As mentioned above, depot naltrexone may improve the compliance difficulties associated with oral formulations. A clinical trial comparing two doses of depot naltrexone (192, 384 mg s.c.) to placebo demonstrated dose-dependent improvement in both treatment retention and opioid abstinence, thereby providing evidence of the efficacy and tolerability of this formulation of naltrexone (Comer et al. 2006).

## Agonist approach: methadone

**Rodents and non-human primates—**Studies since the mid-1970s have investigated the effects of methadone, a high efficacy mu agonist, on self-administration of heroin and other abused opiates in laboratory animals (Griffiths et al. 1976; Jones and Prada 1977; Harrington and Downs 1981; Mello et al. 1983; Negus 2006). Using a discrete-trial choice procedure in which baboons could select either an injection of heroin or delivery of food, Griffiths et al. (1976) found that continuous i.v. infusion of methadone (8.3 mg $kg^{-1}$ $day^{-1}$) for 10 days or longer resulted in a consistent decrease in self-administered heroin and an increase in the number of food deliveries, suggesting that chronic methadone maintenance selectively decreased the reinforcing effects of heroin. Harrington and Downs (1981) also reported that continuous i.v. infusion of methadone (4-24 mg $kg^{-1}$ $day^{-1}$) results in a dose-related decrease in heroin self-administration by rhesus monkeys. However, when the infusion dose of methadone was sufficiently high to reduce self-administration of a broad range of heroin doses, the subjects appeared "debilitated and depressed", suggesting a generalized suppression of behavior rather than a selective effect on heroin reinforcement. Related behavioral side effects of methadone also were observed in a study by Mello et al. (1983) in which self-administration behavior by rhesus monkeys was evaluated during alternating daily sessions of either opiate (heroin or hydromorphone) or food reinforcement. In that study, daily pretreatment with gradually increasing doses of methadone (0.18-11.86 mg $kg^{-1}$ $day^{-1}$ over a 4-month period) did not consistently reduce heroin self-administration even at doses that disrupted food-reinforced responding. The findings of Harrington and Downs (1981) and Mello et al. (1983) are largely consistent with those reported in dogs allowed to self-administer morphine 24 h/day (Jones and Prada 1977). In that study, continuous i.v. infusion of methadone (7.0-48.4 mg $kg^{-1}$ $day^{-1}$ depending on the subject) resulted in a temporary reduction of morphine self-administration that was accompanied by marked sedation. The different profile of effects of methadone maintenance reported in baboons compared to rhesus monkeys and dogs are not easily reconciled, but may be due to methodological factors (e.g., choice vs. non-choice self-administration procedures) and differences in the degree to which subjects were physically dependent on opiates (presumably less severe under conditions of limited heroin access).

Heroin addiction in humans is thought to be maintained both by the positive reinforcing effects of the self-administered drug and by amelioration of the aversive effects induced by opiate withdrawal. Thus, Negus (2006) investigated the effects of continuously infused methadone (0.1-0.56 mg $kg^{-1}$ $h^{-1}$ i.v. in 5-day blocks) on heroin self-administration by rhesus monkeys using a choice procedure involving concurrent scheduling of heroin and food reinforcement.

Subjects initially were studied under a condition of limited heroin access (approximately 100 mg/day), which did not induce appreciable physical dependence. Under these conditions, methadone had little or no effect on either heroin choice or total heroin intake. The subjects were then made physically dependent on heroin by adding supplemental periods of heroin self-administration, which increased the daily heroin intake seven to eightfold. In these heroin-dependent subjects, termination of supplemental heroin increased heroin self-administration during choice periods and induced overt signs of opiate withdrawal. Methadone (0.56 mg $kg^{-1}$ $h^{-1}$) prevented both the withdrawal-associated increase in heroin choice and the emergence of withdrawal signs, findings that appear to model key effects of methadone in heroin-dependent people.

**Human laboratory—**In humans, methadone is administered orally rather than intravenously. An early human laboratory study showed that methadone maintenance (100 mg) substantially decreased self-administration of hydromorphone (4 mg i.v.) compared to the period before methadone administration (Jones and Prada 1975). Similarly, methadone (50-150 mg) maintenance dose-dependently decreased choice to self-administer heroin (10, 20 mg i.v.) and increased choice for an alternative reinforcer (money) in opioid-dependent volunteers (Donny et al. 2005).

**Clinical trial—**Methadone maintenance has been used to effectively decrease opioid use since the 1960s (Dole and Nyswander 1965; see Gonzalez et al. 2002). Essential to methadone's efficacy is dose, as larger methadone doses are more effective than smaller doses in improving clinical outcome (Strain et al. 1999), consistent with the human laboratory data showing that lower methadone doses do not fully block the reinforcing effects of heroin (Donny et al. 2005).

## Partial agonist approach: buprenorphine

**Rodents and non-human primates—**Buprenorphine is a potent, long-acting partial agonist at the mu opioid receptor where it exhibits a profile of mixed agonist and antagonist properties. Like conventional mu antagonists, buprenorphine (i.v.) decreases self-administration of heroin and related mu agonists in non-human primates and rodents (Mello et al. 1983; Winger et al. 1992; Winger and Woods 1996; Mello and Negus 1998; Negus 2006; Chen et al. 2006). Comparing across studies, the results are consistent with the conclusion that buprenorphine induces a relatively selective antagonism of the reinforcing effects of mu agonists. In a recent study by Negus (2006), which involved choice between concurrently available heroin and food, for example, buprenorphine induced a dose-dependent, right-ward shift in the dose-response curve for heroin choice in non-dependent rhesus monkeys—an effect virtually identical to that of naloxone. After the subjects were rendered physically dependent on and then withdrawn from heroin, buprenorphine partially blunted overt signs of withdrawal and withdrawal-induced increases in heroin choice— effects similar to but considerably less pronounced than those of methadone. Aceto (1984) also reported that buprenorphine induced a partial suppression of withdrawal signs in morphine-dependent rhesus monkeys.

As expected of a partial mu agonist, buprenorphine (i.v.) serves as a reinforcer in non-human primates with a history of opioid self-administration (Mello et al. 1981a, 1988; Young et al. 1984; Mello and Mendelson 1985; Lukas et al. 1986; Winger and Woods 2001). Direct comparisons of buprenorphine self-administration with self-administration of other mu agonists suggest that buprenorphine's reinforcing effect is low compared to that of heroin and on a par with the reinforcing effect of methadone (Mello and Mendelson 1985; Mello et al. 1988). Tolerance to the reinforcing effects of buprenorphine also may be greater than tolerance to the effects of heroin or morphine (Winger and Woods 2001). Collectively, these findings

suggest that intravenous buprenorphine functions as a reinforcer, but does not induce abuse to a degree comparable to heroin.

**Human laboratory—**The first laboratory studies of buprenorphine demonstrated that maintenance on subcutaneous buprenorphine (8 mg) decreased heroin self-administration (up to 13.5 mg i.v.) by 69-98% compared to placebo maintenance in detoxified heroin abusers (Mello and Mendelson 1980; Mello et al. 1982). The subjective effects produced by this dose of buprenorphine was approximately equivalent to that produced by 40-60 mg of methadone (Jasinksi et al. 1978).

More recent studies with buprenorphine utilized a sublingual tablet formulation, which has lower bioavail-ability than parenteral formulations but is the only preparation currently available in the USA. The influence of sublingual buprenorphine (8 and 16 mg) on heroin self-administration (6.25 to 25 mg i.v.) have been assessed in opioid-dependent research volunteers. The reinforcing effects of an intermediate dose of heroin (12.5 mg) was significantly lower when participants were maintained on the higher dose of buprenorphine (16 mg), but buprenorphine did not significantly block heroin self-administration at the other dose combinations (Comer et al. 2001). These data, which differ from those reported by Mello and colleagues, most likely reflect the lower potency and bioavailability of sublingual compared to subcutaneous buprenorphine. In addition, the timing of the buprenorphine administration (19 h before heroin self-administration sessions) likely resulted in the limited effectiveness of buprenorphine in the study by Comer and colleagues.

In the laboratory, buprenorphine (0.125 to 8 mg i.v.) was not self-administered more than placebo by opioid-dependent volunteers, but detoxified heroin users self-administered higher doses of buprenorphine (0.5 to 8 mg i.v.) than placebo, demonstrating abuse potential by the i.v. route of administration for this group (Comer et al. 2002a, 2005, 2008b; Comer and Collins 2002). These latter findings are generally consistent with the results obtained in self-administration studies with animals and appear to be borne out by international epidemiological evidence of i.v. buprenorphine abuse (Obadia et al. 2001; Vidal-Trecan et al. 2003)

In light of the abuse potential for buprenorphine by the i.v. route, sublingual formulations combining naloxone with buprenorphine have been developed and are currently the primary formulation used in the USA. Naloxone has low bioavailability orally, but is effective as an opioid antagonist when given parenterally. Therefore, if taken sublingually as prescribed, naloxone should not interfere with the effects of buprenorphine. If buprenorphine/naloxone is crushed and used either intranasally or intravenously, however, the antagonist effects of naloxone should blunt the reinforcing effects of buprenorphine. Furthermore, ifdiverted for illicit use by heroin-dependent individuals, the naloxone component of the formulation would be expected to precipitate opioid withdrawal symptoms. The addition of naloxone, therefore, should reduce the abuse liability of buprenorphine both by blunting the acute effects of parenteral buprenorphine and by precipitating withdrawal symptoms in dependent individuals.

A laboratory comparison of a range of buprenorphine/naloxone doses combinations on intranasal heroin self-administration (12.5 to 50 mg) by opioid-dependent volunteers demonstrated that 8/2 mg and 32/8 mg buprenorphine/naloxone combinations were well tolerated and decreased heroin's reinforcing and subjective effects compared to a low dose of buprenorphine/naloxone (2/0.5 mg; Comer et al. 2005). Thus, the combination appears to be efficacious at sufficient dose levels.

There is, however, little indication from human laboratory studies to suggest that the combination is less reinforcing than buprenorphine alone. In detoxified heroin abusers, buprenorphine/naloxone combinations (2/0.5 and 8/2 mg) produced fewer opioid-related

subjective effects, but were as reinforcing as buprenorphine alone (2 and 8 mg; Comer and Collins 2002). It may be that buprenor-phine/naloxone combinations would have less abuse liability if opioid-dependent populations were studied. Further research on this key population is clearly needed.

**Clinical trial—**At certain doses, buprenorphine is as efficacious as methadone in reducing opiate use and promoting treatment retention (see Johnson et al. 2000). An advantage of buprenorphine over methadone is that due to buprenorphine's long duration of action and ceiling effect on agonist activity (Greenwald et al. 2007), daily dosing is not required. Patients who receive high doses of buprenorphine two or three times per week show comparable abstinence rates as those receiving lower doses of buprenorphine on a daily basis (Marsch et al. 2005). The efficacy of combining naloxone with buprenorphine to decrease the abuse liability of intravenous administration is still under investigation, but recent evidence suggests that buprenorphine/naloxone tablets are less preferred and carry a lower street price than buprenorphine alone in a population of untreated i.v. opioid users (Alho et al. 2007), consistent with the human laboratory data.

### Summary

Although human and animal preclinical self-administration models predicted naltrexone's pharmacological blockade of heroin's reinforcing effects, naltrexone is not an effective pharmacotherapy because most patients do not comply with prescribed treatment regimens. These data emphasize that the pharmacological properties of a medication cannot be considered in isolation of compliance issues. More recent advances in depot formulations of naltrexone may effectively address this issue.

Poor compliance with oral naltrexone also highlights the benefits of using full or partial agonists as opposed to antagonists in treating drug dependence. Human and animal preclinical models of heroin self-administration predicted the clinical effects of both methadone and buprenorphine for which compliance is less of an issue. In non-human primates, methadone maintenance decreases heroin self-administration most selectively when animals were opioid-dependent and undergoing withdrawal (Negus 2006). In parallel, human laboratory and clinical trial studies in opioid-dependent individuals demonstrate that long-term maintenance on methadone dose-dependently decreases opioid self-administration in the laboratory as well as opioid abuse in the natural ecology. Similarly, buprenorphine maintenance decreases heroin self-administration in the rodent, non-human primate, and human laboratory, consistent with improved retention rates and drug toxicology results in the clinic. Buprenorphine's antagonist-like properties attenuate the effects of heroin and other mu agonists, while its agonist-like properties likely contribute to its improved compliance compared to conventional mu antagonists (see Walsh and Eissenberg 2003). These agonist effects also emphasize the importance of assessing the abuse liability of potential treatment medications in laboratory studies, so adaptations could be made before clinical use (such as combining naloxone and buprenorphine).

## Cocaine self-administration and medication effects

There have been a vast number of medications tested to treat cocaine dependence, including antidepressants, anticonvulsants, antipsychotics, and mood stabilizers, among others (see Grabowski et al. 2004), but none have been efficacious, and none have been Food and Drug Administration (FDA)-approved for this indication. Given the success in opioid pharmacotherapy, it is useful to consider a parallel approach for the treatment of cocaine dependence. Thus, we will describe an antagonist, agonist, and partial agonist approach to modulating cocaine self-administration, with the caveat that these terms are imprecise pharmacologically because multiple neurotransmitter systems mediate cocaine's reinforcing

effects. Dopamine plays an important (Ritz et al. 1987; Bergman et al. 1989; Madras et al. 1989) but, by no means, exclusive role in mediating cocaine reinforcement, so antagonists at this one receptor class, for example, are not truly cocaine antagonists. Nonetheless, there is heuristic value in comparing the successes seen with opioid treatment to the approach used for cocaine.

## "Antagonist" approach: ecopipam (SCH 39166)

The two main families of dopamine receptor subtypes (D1 and D2; Jackson and Westlind-Danielsson 1994; Kebabian and Calne 1979) both contribute to cocaine's reinforcing effects (Spealman et al. 1992; Woolverton and Johnson 1992), yet maintenance on D2 antagonists can produce permanent extrapyramidal side effects, so the following discussion will primarily focus on studies testing D1 receptor antagonists.

**Rodents and non-human primates—**Acute pretreatment with D1 antagonists appears to block cocaine's reinforcing effects in rats (Caine and Koob 1994; Depoortere et al. 1993; Hubner and Moreton 1991) and monkeys (Bergman et al. 1990; Campbell et al. 1999) in a partially surmountable manner. Some studies report that acute pretreatment with the D1 antagonist, SCH 23390 (Howell and Byrd 1991; Woolverton 1986; Woolverton and Virus 1989) or SCH 39166 (ecopipam; Winger 1994; Platt et al. 2001) only suppressed cocaine self-administration at doses that produced catalepsy or decreased responding for food, yet others indicate that D1 antagonists selectively alter cocaine self-administration at doses that do not result in motor incapacitation or impaired responding for food in rats (Caine and Koob 1994; McGregor and Roberts 1993) or monkeys (Kleven and Woolverton 1990). In general, however, such selectivity is observed over a relatively narrow dose range (see review by Platt et al. 2002).

Chronic administration of dopamine antagonists over days or weeks often results in a diminution or reversal of the effects seen after acute administration. Although acute administration of dopamine D1 or D2 antagonists can block cocaine's reinforcing and discriminative-stimulus effects, repeated antagonist administration can increase cocaine's reinforcing (self-administration) and rewarding (conditioned place preference) effects in rats (Emmett-Oglesby and Mathis 1988; Kosten et al. 1996; Kosten 1997).

Additionally, termination of chronic dopamine antagonist administration may produce a pattern of effects different from that seen after acute administration. In rhesus monkeys, acute pretreatment with a D1 antagonist initially decreased cocaine self-administration in two out of four monkeys, but after antagonist maintenance was terminated, self-administration of cocaine was increased in three out of four monkeys compared to the period before antagonist exposure (Kleven and Woolverton 1990). That is, doses of cocaine that maintained relatively low levels of self-administration maintained higher levels of self-administration after chronic exposure to a D1 antagonist. Further, termination of chronic D1 antagonist administration in rodents was associated with a leftward shift in the dose-response curve for the discriminative-stimulus and locomotor stimulant effects of cocaine and other indirect or direct dopamine agonists (Barone et al. 1988; Braun et al. 1997; Vaccheri et al. 1987). These behavioral shifts were associated with an increased density of D1 receptors (Creese and Chen 1985; Gui-Hua et al. 1992; Hess et al. 1986) and enhanced D1 receptor sensitivity (White et al. 1998). Overall, the data suggest that maintenance on a D1 antagonist may lead to a persistent enhancement of the reinforcing and subjective effects of cocaine after antagonist administration is terminated.

**Human laboratory—**Data from the human laboratory are consistent with these preclinical findings. Acute pretreatment with the selective D1 antagonist, ecopipam (10, 25, 100 mg p.o.), dose-dependently decreased the effects of cocaine (30 mg i.v.) on ratings of "high" and "good

drug effect" and decreased the reported desire for cocaine in cocaine-dependent research volunteers (Romach et al. 1999). By contrast, maintenance on ecopipam (10-100 mg p.o. for 5-7 days before smoked or i.v. cocaine) either did not decrease cocaine's subjective effects (0-50 mg/70 kg i.v.; Nann-Vernotica et al. 2001) or was shown to increase self-administration of a low cocaine dose (12 mg) while also increasing ratings of "high" and "good drug effect" as well as the perceived quality of larger cocaine doses (25, 50 mg; Haney et al. 2001).

**Clinical data—**In accordance, controlled, multi-site clinical trial testing ecopipam maintenance in cocaine-dependent treatment seekers was terminated due to a lack of efficacy (see Grabowski et al. 2000). Thus, the effects of ecopipam maintenance in the clinic are consistent with human cocaine self-administration models and are consistent with primate and rodent cocaine self-administration procedures when the medication was administered repeatedly.

## "Agonist" approach: modafinil

The mechanism by which the FDA-approved wake-promoting agent, modafinil, interacts with cocaine has not been established. Many (but not all) of modafinil's neurochemical effects overlap with those of cocaine. Thus, modafinil occupies both dopamine and norepinephrine transporter sites (Mignot et al. 1994), and clinically relevant doses of modafinil increase extracellular dopamine levels (Madras et al. 2006). Further, modafinil enhances glutamate release and inhibits both γ-aminobutyric acid release (Ferraro et al. 1999) and the firing of midbrain dopamine neurons (Korotkova et al. 2007). Note that although D-amphetamine may be a closer neurochemical analogue to cocaine than modafinil to demonstrate an agonist approach and D-amphetamine has shown promise preclinically and clinically for the treatment of cocaine dependence (see Grabowski et al. 2004), this medication has not been tested in the human laboratory, so does not follow the format of the other medications discussed.

In terms of abuse liability, human volunteers self-administer modafinil more than placebo under certain conditions (Stoops et al. 2005), but most studies suggest that the medication has low abuse liability even among drug abusers (Jasinski 2000; Rush et al. 2002a, b), and post-marketing surveillance indicate modafinil misuse is low (see Myrick et al. 2004). The presence of positive mood effects, in fact, is likely a positive feature in that it improves medication compliance.

**Rodents and non-human primates—**In rats, acute modafinil pretreatment (up to 128 mg/kg) had no effect on cocaine self-administration (Deroche-Gamonet et al. 2002), but the effects of chronic modafinil administration on cocaine reinforcement has not been studied. There are also no data, to our knowledge, on modafinil's effects on cocaine self-administration by non-human primates.

**Human laboratory—**In human laboratory studies, modafinil produced stimulant-like effects and improved cognitive performance when individuals were tired (Hart et al. 2008). The first human laboratory studies combining modafinil with cocaine (i.v.) demonstrated that modafinil was not only safe in combination with cocaine but that it also decreased cocaine's intoxicating and cardiovascular effects (Dackis et al. 2003; Malcolm et al. 2006; Donovan et al. 2005). A recent human study of smoked cocaine self-administration demonstrated that modafinil maintenance (200, 400 mg/day) decreased high-dose cocaine self-administration (25, 50 mg) as well as cocaine's intoxicating (e.g., high, good drug effect) and cardiovascular effects.

**Clinical trial—**A pilot clinical trial showed that modafinil (400 mg/day) significantly reduced the number of cocaine-positive urines (Dackis et al. 2005), consistent with the laboratory data. A more recent multi-site clinical trial appears to confirm modafinil's efficacy to facilitate

abstinence in cocaine-dependent patients provided that patients were not also alcohol-dependent or did not have a history of alcohol dependence (F. Vocci, 8/07, personal communication).

## Partial agonist approach: aripiprazole

**Rodents and non-human primates—**Various dopamine D1- and D2-like partial agonists have been proposed as candidate pharmacotherapies for cocaine addiction based on their ability to modulate i.v. cocaine self-administration in rodents and non-human primates (see review by Platt et al. 2002). Surprisingly, there appears to be only one published report that specifically examined the effects of aripiprazole, an atypical D2-like partial agonist with low incidence of extrapyramidal side effects, in rats trained to self-administer cocaine (Feltenstein et al. 2007). Although acute aripiprazole pretreatment (0.5-2.5 mg/kg, i.p.) significantly attenuated the reinstatement of extinguished cocaine seeking after the administration of cocaine or cocainepaired cues, aripiprazole did not significantly reduce self-administration of cocaine. A trend toward increased intake of cocaine at higher doses of aripiprazole is consistent with findings using conventional D2-like partial agonists, such as terguride, in rats (e.g., Pulvirenti et al. 1998).

**Human laboratory—**There are few published studies available with aripiprazole and cocaine to date. There is one human laboratory study with oral D-amphetamine showing that acute aripiprazole pretreatment (2.5 to 15 mg/day) decreased the discriminative-stimulus and subjective effects of this drug (Lile et al. 2005). In terms of cocaine, only preliminary data from an ongoing self-administration study are available to date. In this study by Haney and colleagues, cocaine-dependent participants were maintained on both placebo and aripiprazole (15 mg/day) capsules for 17 days before the onset of cocaine self-administration sessions (it takes 2 weeks to achieve steady state with aripiprazole). Smoked cocaine dose-response curves (0, 12, 25, 50 mg) were determined using a progressive-ratio schedule of reinforcement. Preliminary data show that aripiprazole maintenance robustly increased cocaine (12, 25 mg) self-administration compared to placebo maintenance. Aripiprazole did not appear to alter cocaine intoxication, although it increased baseline rates of anxiety.

**Clinical trial—**To date, there are no published clinical trials testing aripiprazole to treat cocaine dependence. However, a recent clinical trial for amphetamine dependence was terminated early because the aripiprazole group showed greater amphetamine use than those receiving placebo (Tiihonen et al. 2007), which appears consistent with the human laboratory findings with cocaine.

## Summary

Overall, data from non-human animal and human laboratory studies are consistent with clinical outcome. Acute ecopipam administration blocked cocaine's reinforcing effects in rats and monkeys and decreased cocaine's positive subjective effects in human subjects. When ecopipam was given chronically, however, it increased cocaine self-administration in animal and human laboratory studies and, predictably, did not improve clinical outcome in individuals seeking treatment for their cocaine use in clinical trials. Similarly, aripiprazole maintenance increased cocaine self-administration in the laboratory and appeared to worsen outcome for amphetamine treatment (no clinical data on cocaine are available to date). Note that it does not appear that either aripiprazole or ecopipam increased cocaine self-administration by antagonizing the reinforcing effects of cocaine because cocaine "high" was not blunted by either ecopipam or aripiprazole maintenance compared to placebo. That is, if these medications increased cocaine self-administration in an attempt to overcome a blockade of reinforcement, one would expect to see a parallel decrease in ratings of cocaine intoxication. Rather, the fact that the acute effects of ecopipam and aripiprazole in combination with psychostimulants were

in an opposite direction as when these medications were given repeatedly suggests that maintenance on dopamine antagonists or partial agonists may enhance the reinforcing effects of psychostimulants.

The clinical data with modafinil, although preliminary, appear to validate the human laboratory model of cocaine self-administration for medications development by demonstrating that modafinil maintenance decreases high dose cocaine self-administration in the laboratory and decreases cocaine use in the clinic. No studies in rodent and non-human primates have yet been conducted in which modafinil is administered repeatedly before cocaine self-administration. These studies are essential to validate the preclinical self-administration model relevant to cocaine pharmacotherapy.

## Overall conclusions and recommendations

### Self-administration versus other models

The self-administration model clearly predicts medications that effectively treat opioid dependence and appears also to be the best behavioral paradigm for predicting medications to treat cocaine dependence. Preclinical studies often assess the effects of acute medication pretreatment on cocaine self-administration, while the majority of human studies have been either open-label clinical trials or laboratory studies characterizing medication effects on cocaine craving or “high,” but not cocaine self-administration. Cocaine’s subjective effects contribute to its abuse liability, so it is reasonable to presume that modulating these effects with medications would predict clinical outcome. However, this assumption is not supported empirically.

Although there are examples in which medications, such as amantadine, bromocriptine, and phenytoin, failed to decrease cocaine intoxication in the laboratory (Collins et al. 2003; Preston et al. 1992; Sofuoglu et al. 1999) and also failed to decrease cocaine use in clinical trials (Kampman et al. 2006; de Lima et al. 2002; Gorelick and Wilkins 2006), overall, cocaine’s subjective effects appear to be more sensitive to modulation by medications, resulting in a high rate of false positives when this is the primary outcome measured (see also Comer et al. 2008a). A vast array of compounds including gabapentin, desipramine, pergolide, risperidone, ecopipam, selegeline, venlafaxine, and naltrexone, for example, have been shown to decrease ratings of a cocaine intoxication or cocaine-elicited craving in the laboratory (Hart et al. 2004, 2007a, b; Fischman et al. 1990; Haney et al. 1998; Romach et al. 1999; Newton et al. 1999; Foltin et al. 2003; Sofuoglu et al. 2003), yet none of these compounds decreased cocaine use in controlled clinical trials (Bisaga et al. 2006; Campbell et al. 2003; Malcolm et al. 2000; Grabowski et al. 2000; Elkashef et al. 2006; Ciraulo et al. 2005; Grassi et al. 2007).

By contrast, cocaine self-administration is extraordinarily difficult to disrupt. Even medications that substantially decrease cocaine craving or its “good drug effect” rarely decrease cocaine self-administration (e.g., Fischman et al. 1990; Haney et al. 1999; Hart et al. 2004, 2007a, b). In fact, no medication has robustly and selectively decreased cocaine self-administration in the human laboratory until a recent study with modafinil, which attenuated both cocaine’s reinforcing and subjective effects (Hart et al. 2008). Two other medications, baclofen and buprenorphine, have been shown to significantly decrease cocaine use as well, but these effects were either limited to a low dose of cocaine or reflected an apparent leftward shift in the cocaine dose-response curve. Specifically, baclofen produced a small but significant decrease in low-dose cocaine self-administration (Haney et al. 2006). Baclofen has also shown promise in a pilot clinical trial for cocaine dependence (Shoptaw et al. 2003), but more recent clinical work suggests that baclofen’s effects may not be sufficiently robust to reduce ongoing cocaine abuse (S. Shoptaw, 3/06, personal communication). Buprenorphine, the only other medication shown to significantly decrease high-dose cocaine self-administration, appeared to

do so by significantly enhancing cocaine intoxication, mimicking a cocaine-heroin "speedball" effect (Foltin and Fischman 1994), which is less than ideal for a potential treatment medication.

To summarize, animal self-administration models help eliminate from consideration candidate medications that display undesirable properties (e.g., high abuse potential, side effects; Platt et al. 2002), and human self-administration studies predict medication failure or success in the clinic with much better accuracy than studies that solely rely on self-reported subjective effects or measures of craving. The large number of false positives obtained in studies that do not assess self-administration emphasizes the importance of this measure when investigating potential pharmacotherapies.

## Medication maintenance

Clinically useful medications targeting drug dependence require long-term treatment regimens to be maximally effective. Yet, evaluations of potential pharmacotherapies for cocaine and opiate dependence in animal drug self-administration studies most often utilize acute medication pretreatment paradigms. One factor that may be essential to improving the predictive validity of laboratory self-administration models is the duration of medication administration (see Mello and Negus 1996; McCance-Katz et al. 2001; Grabowski et al. 2004). Treatment durations of just several days can reveal changes in the effects of a candidate medication that might not be anticipated on the basis of its acute effects. Some medications only decrease cocaine self-administration when given acutely, while others require repeated administration before selectively attenuating drug self-administration: Acute D-amphetamine administration suppressed both food-intake and cocaine self-administration in non-human primates, but with repeated D-amphetamine administration, tolerance developed to the suppression of food intake, but not the suppression of cocaine self-administration (Negus and Mello 2003). Thus, rodent, non-human primate, and human laboratory models may gain improved predictive power by adopting protocols that include longer periods of medication treatment.

## Alternative reinforcers

The majority of drug self-administration studies in laboratory animals have not provided explicit alternative reinforcers as part of the experimental design, leading to the suggestion that animal self-administration studies model populations at higher risk for drug addiction compared to the general population, i.e., those at risk for drug use may be in an environment with few other sources of reinforcement (see Ahmed 2005). As most individuals who use drugs are faced with at least minimally reinforcing alternatives to drug use, animal self-administration procedures involving drug and non-drug alternatives provide a meaningful paradigm for evaluating the impact of such alternatives. A consistent finding in such studies is that increasing the relative availability of alternative reinforcers results in a reduction of drug choice (Nader and Woolverton 1992; Woolverton et al. 1997; Campbell and Carroll 2000). Similarly, increasing the value of an alternative reinforcer in human studies decreases drug choice (Higgins et al. 1994; Hatsukami et al. 1994), although the value of the alternative reinforcer appears to have less impact once drug (particularly cocaine) self-administration is initiated (Donny et al. 2003).

Medications that decrease the reinforcing effects of heroin or cocaine should shift choice from these drugs to non-drug alternatives. Shifts of this type have been observed consistently for heroin self-administration in both animal and human laboratory studies, supporting the continued use of choice procedures for evaluating potential pharmacotherapies for cocaine or heroin abuse in both the animal and human laboratory setting. Few medications have selectively and robustly shifted cocaine self-administration, but it may be that this behavior would be more sensitive to medication effects if alternative reinforcers were immediate (as the cocaine

reinforcer is). For example, non-human primates responding to receive either cocaine or an alternative reinforcer chose less cocaine if the delivery of the alternative reinforcer was immediate compared to when the delivery of the alternative reinforcer was delayed (Woolverton and Anderson 2006). In most human laboratory procedures, the alternative reinforcer is not available until completion of the study. Additional research is needed to test the impact of immediate non-drug reinforcers on cocaine choice compared to delayed reinforcers to develop a more comprehensive characterization of how potential medications influence cocaine self-administration.

### Treatment-seeking versus non-treatment-seeking subjects

Some have argued that a general flaw of laboratory models is that human research volunteers (as well as laboratory animals) are not motivated to use less drug (Marlatt 1996). In addition, self-administration procedures in both humans and laboratory animals typically focus on stable patterns of drug intake, which do not model the transition from casual to compulsive drug use or relapse (see Ahmed 2005). Although modeling specific features of the addiction cycle is necessary for understanding the neurobiology of addiction, it is not necessarily essential for developing medications to target compulsive drug use. An effective model need not be identical to behavior in the natural ecology to *predict* behavior in the natural ecology. Thus, as demonstrated most clearly by heroin self-administration studies, medications that decrease heroin's direct reinforcing effects in humans or laboratory animal models accurately predict clinical outcome despite the fact that the animals have stable patterns of drug intake and that the human volunteers are not seeking treatment.

### Ethics of self-administration models

It is critical to consider the ethics of using laboratory animals, particularly non-human primates, and humans in translational self-administration studies. In addressing this question, one must also consider the ethics of *not* determining the safety and efficacy of a medication that may contribute to the treatment of cocaine or heroin dependence (Fischman and Johanson 1998). Non-human primates are most closely related to humans in terms of neurochemistry, pharmacokinetics, and behavior and are sufficiently distinct from rodents to play an essential role in medications development (see Weerts et al. 2007). Laboratory models using human research volunteers who are unambiguous about their intent to continue to use cocaine or heroin have been used safely for more than 30 years (Fischman et al. 1976; Meyer and Mirin 1979) and are an important precursor to exposing hundreds of patients to a medication with unknown effects on drug use. Given that the self-administration model is more predictive of clinical response than other laboratory procedures, studying the effects of a potential medication on a drug's reinforcing effects under carefully controlled conditions in a relatively small number of individuals appears to be both scientifically meaningful and ethical.

### Suggestions for future research

To confirm the validity of cocaine self-administration models for medications development, future studies should use a top-down approach to test the few laboratory medications that have shown some clinical success. Rodent and non-human primate studies need to be conducted with modafinil maintenance (not pretreatment) to compare to the clinical data, while human laboratory studies testing sustained-release D-amphetamine's effects on cocaine self-administration should be done (see Grabowski et al. 2004). The fact that both modafinil and D-amphetamine have shown clinical promise suggests that agonist-like medications show the most promise for treating cocaine dependence.

In addition, opioid data illustrate that treatment approaches obviating compliance problems (e.g., depot naltrexone) are an important treatment goal. A long-lasting, non-pharmacological approach that has tremendous potential for treating cocaine dependence is vaccination. Cocaine

vaccines decrease cocaine self-administration in rats (Kantak 2003) and substantially blunt ratings of smoked cocaine "high" (by 50-70% depending on cocaine dose) in cocaine-dependent research volunteers (Haney et al., CPDD presentation 2006). Cocaine self-administration in vaccinated volunteers has not yet been tested, but there are clinical indications that the vaccine is safe and well tolerated in cocaine-dependent patients (Kosten et al 2002; Martell et al. 2005), and the cocaine vaccine will undergo further clinical testing. Not all individuals produce sufficient antibody titers in response to vaccination, but among those who do, an enormous benefit is that the response to cocaine appears to be blunted for at least several weeks (Haney and Kosten 2005). Thus, antibodies may be able to prevent a slip or single use of cocaine from becoming a full-scale relapse and could provide a period of time in which a motivated patient could profit from psychosocial treatment and develop cognitive strategies to avoid future drug use.

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## References

Aceto MD. Characterization of prototypical opioid antagonists, agonist-antagonists, and agonists in the morphine-dependent rhesus monkey. Neuropeptides 1984;5:15–18. [PubMed: 6099486]

Ahmed SH. Imbalance between drug and non-drug reward availability: a major risk factor for addiction. Eur J Pharmacol 2005;526:9–20. [PubMed: 16263108]

Alho H, Sinclair D, Vuori E, Holopainen A. Abuse liability of buprenorphine-naloxone tablets in untreated IV drug users. Drug Alcohol Depend 2007;88:75–78. [PubMed: 17055191]

Altman JL, Meyer RE, Mirin SM, McNamee HB. Opiate antagonists and the modification of heroin self-administration behavior in man: an experimental study. Int J Addict 1976;11:485–499. [PubMed: 184054]

Balster RL. Drug abuse potential evaluation in animals. Br J Addict 1991;86:1549–1558. [PubMed: 1786486]

Barone P, Tucci I, Parashos SA, Chase TN. Supersensitivity to a D-1 dopamine receptor agonist and subsensitivity to a D-2 receptor agonist following chronic D-1 receptor blockade. Eur J Pharmacol 1988;49:225–232. [PubMed: 3261693]

Bergman J, Madras BK, Johnson SE, Spealman RD. Effects of cocaine and related drugs in nonhuman primates. III. Self-administration by squirrel monkeys. J Pharmacol Exp Ther 1989;251:150–155. [PubMed: 2529365]

Bergman J, Kamien JB, Spealman RD. Antagonism of cocaine self-administration by selective dopamine D(1) and D(2) antagonists. Behav Pharmacol 1990;1:355–363. [PubMed: 11175420]

Bertalmio AJ, Woods JH. Reinforcing effect of alfentanil is mediated by mu opioid receptors: apparent pA2 analysis. J Pharmacol Exp Ther 1989;251:455–460. [PubMed: 2553919]

Bigelow, GE.; Walsh, SL. Evaluation of potential pharmacotherapies: response to cocaine challenge in the human laboratory. In: Higgins, ST.; Katz, JL., editors. Cocaine abuse: behavior, pharmacology, and clinical applications. Elsevier; Amsterdam: 1998. p. 209-238.

Bisaga A, Aharonovich E, Garawi F, Levin FR, Rubin E, Raby WN, Nunes EV. A randomized placebo-controlled trial of gabapentin for cocaine dependence. Drug Alcohol Depend 2006;81:267–274. [PubMed: 16169160]

Blumberg H, Dayton HB. Naloxone, naltrexone, and related noroxymorphones. Adv Biochem Psychopharmacol 1974;8:33–43. [PubMed: 4794989]

Brady, JV.; Griffiths, RR.; Hienz, RD.; Ator, NA.; Lukas, SE.; Lamb, RJ. Assessing drugs for abuse liability and dependence potential in laboratory primates. In: Bozarth, MA., editor. Methods of assessing the reinforcing properties of abused drugs. Springer; Berlin: 1987. p. 45-86.

Braun AR, Laruelle M, Mouradian MM. Interactions between D1 and D2 dopamine receptor family agonists and antagonists: the effects of chronic exposure on behavior and receptor binding in rats and their clinical implications. J Neural Transm 1997;104:341–362. [PubMed: 9295170]

Caine SB, Koob GF. Effects of dopamine D-1 and D-2 antagonists on cocaine self administration under different schedules of reinforcement in the rat. J Pharmacol Exp Ther 1994;270:209–218. [PubMed: 8035317]

Campbell UC, Carroll ME. Reduction of drug self-administration by an alternative non drug reinforcer in rhesus monkeys: magnitude and temporal effects. Psychopharmacology 2000;147:418–425. [PubMed: 10672636]

Campbell UC, Lac ST, Carroll ME. Effects of baclofen on maintenance and reinstatement of intravenous cocaine self-administration in rats. Psychopharmacology 1999;143:209–214. [PubMed: 10326784]

Campbell J, Nickel E, Penick EC, Wallace D, Gabrielle WF, Rowe C, Liskow B, Powell BJ, Thomas HM. Comparison of desipramine or carbamezepine to placebo for crack cocaine-dependent patients. Am J Addict 2003;12:122–136. [PubMed: 12746087]

Capone R, Brahen L, Condren R, Kordal N, Melchionda R, Peterson M. Retention and outcome in a narcotic antagonist treatment program. J Clin Psychol 1986;42:825–833. [PubMed: 3760220]

Chen SA, O'Dell LE, Hoefer ME, Greenwell TN, Zorrilla EP, Koob GF. Unlimited access to heroin self-administration: independent motivational markers of opiate dependence. Neuro-psychopharmacology 2006;31:2692–2707.

Ciraulo DA, Sarid-Segal O, Knapp CM, Ciraulo AM, LoCastro J, Bloch DA, Montgomery MA, Leiderman DB, Elkashef A. Efficacy screening trials of paroxetine, pentoxifylline, riluzole, pramipexole and venlafaxine in cocaine dependence. Addiction 2005;100:12–22. [PubMed: 15730346]

Collins ED, Vosburg SK, Hart CL, Haney M, Foltin RW. Amantadine does not modulate reinforcing, subjective, or cardiovascular effects of cocaine in humans. Pharmacol Biochem Behav 2003;76:401–407. [PubMed: 14643838]

Comer SD, Collins ED. Self-administration of intravenous buprenorphine and the buprenorphine/naloxone combination by recently detoxified heroin abusers. J Pharmacol Exp Ther 2002;303:695–703. [PubMed: 12388653]

Comer SD, Collins ED, Fischman MW. Choice between money and intranasal heroin in morphine-maintained humans. Behav Pharmacol 1997;8:677–690. [PubMed: 9832953]

Comer SD, Collins ED, Wilson ST, Donovan MR, Foltin RW, Fischman MW. Effects of an alternative reinforcer on intravenous heroin self-administration by humans. Euro J Pharmacol 1998;345:13–26.

Comer SD, Collins ED, MacArthur RB, Fischman MW. Comparison of intravenous and intranasal heroin self-administration by morphine-maintained humans. Psychopharmacology 1999;143:327–338. [PubMed: 10367549]

Comer SD, Collins ED, Fischman MW. Buprenorphine sublingual tablets: effects on IV heroin self-administration by humans. Psychopharmacology 2001;154:28–37. [PubMed: 11292003]

Comer SD, Collins ED, Fischman MW. Intravenous buprenorphine self-administration by detoxified heroin abusers. J Pharmacol Exp Ther 2002a;301:266–276. [PubMed: 11907183]

Comer SD, Collins ED, Kleber HD, Nuwayser ES, Kerrigan JH, Fischman MW. Depot naltrexone: long-lasting antagonism of the effects of heroin in humans. Psychopharmacology 2002b;159:351–360. [PubMed: 11823887]

Comer SD, Walker EA, Collins ED. Buprenorphine/naloxone reduces the reinforcing and subjective effects of heroin in heroin-dependent volunteers. Psychopharmacology 2005;181:664–675. [PubMed: 16025322]

Comer SD, Sullivan MA, Yu E, Rothenberg JL, Kleber HD, Kampman K, Dackis C, O'Brien CP. Injectable, sustained-release naltrexone for the treatment of opioid dependence. Arch Gen Psychiatry 2006;63:210–218. [PubMed: 16461865]

Comer SD, Ashworth JB, Foltin RW, Johanson C-E, Zacny JP, Walsh SD. The role of human drug self-administration procedures in the development of medications. Drug Alcohol Depend. 2008ain press

Comer SD, Sullivan MA, Whittington RA, Vosburg SK, Kowalczyk WJ. Abuse liability of prescription opioids compared to heroin in morphine-maintained heroin abusers. Neuropsycho-pharmacology. 2008b(in press) DOI 10.1038/sj.npp.1301479

Corrigall WA, Coen KM. Fixed-interval schedules for drug self-administration in the rat. Psychopharmacology 1989;99:136–139. [PubMed: 2506599]

Creese I, Chen A. Selective D-1 dopamine receptor increase following chronic treatment with SCH 23390. Eur J Pharmacol 1985;109:127–128. [PubMed: 2859993]

Dackis CA, Lynch KG, Yu E, Samaha FF, Kampman KM, Cornish JW, Rowan A, Poole S, White L, O'Brien CP. Modafinil and cocaine: a double-blind, placebo-controlled drug interaction study. Drug Alcohol Depend 2003;70:29–37. [PubMed: 12681523]

Dackis CA, Kampman KM, Lynch KG, Pettinati HM, O'Brien CP. A double-blind, placebo-controlled trial of modafinil for cocaine dependence. Neuropsychopharmacology 2005;30:205–211. [PubMed: 15525998]

de Lima MS, de Oliveira Soares BG, Reisser AA, Farrell M. Pharmacological treatment of cocaine dependence: a systematic review. Addiction 2002;97:931–949. [PubMed: 12144591]

Deneau GA, Yanagita T, Seevers MH. Self-administration of psychoactive substances by the monkey. Psychopharmaolcogia 1969;61:30–48.

Depoortere RY, Li DH, Lane JD, Emmett-Oglesby MW. Parameters of self-administration of cocaine in rats under a progressive-ratio schedule. Pharmacol Biochem Behav 1993;45:539–548. [PubMed: 8332614]

Deroche-Gamonet V, Darnaudéry M, Bruins-Slot L, Piat F, Le Moal M, Piazza PV. Study of the addictive potential of modafinil in naive and cocaine-experienced rats. Psychopharmacology 2002;161:387–395. [PubMed: 12073166]

Dole VP, Nyswander ME. A medical treatment for diacetylmorphine (heroin) addiction: a clinical trial with methadone hydrochloride. JAMA 1965;193:80–84.

Donny EC, Bigelow GE, Walsh SL. Choosing to take cocaine in the human laboratory: effects of cocaine dose, inter-choice interval, and magnitude of alternative reinforcement. Drug Alcohol Depend 2003;69:289–301. [PubMed: 12633915]

Donny EC, Bigelow GE, Walsh SL. Assessing the initiation of cocaine self-administration in humans during abstinence: effects of dose, alternative reinforcement, and priming. Psychopharmacology 2004;172:316–323. [PubMed: 14647955]

Donny EC, Brasser SM, Bigelow GE, Stitzer ML, Walsh SL. Methadone doses of 100 mg or greater are more effective than lower doses at suppressing heroin self-administration in opioid-dependent volunteers. Addiction 2005;100:1496–1509. [PubMed: 16185211]

Donovan JL, DeVane CL, Malcolm RJ, Mojsiak J, Chiang CN, Elkashef A, Taylor RM. Modafinil influences the pharmacokinetics of intravenous cocaine in healthy cocaine-dependent volunteers. Clin Pharmacokinet 2005;44:753–765. [PubMed: 15966757]

Dudish-Poulsen SA, Hatsukami DK. Dissociation between subjective and behavioral responses after cocaine stimuli presentations. Drug Alcohol Depend 1997;47:1–9. [PubMed: 9279492]

Elkashef A, Fudala PJ, Gorgon L, Li SH, Kahn R, Chiang N, Vocci F, Collins J, Jones K, Boardman K, Sather M. Double-blind, placebo-controlled trial of selegiline transdermal system (STS) for the treatment of cocaine dependence. Drug Alcohol Depend 2006;85:191–197. [PubMed: 16730924]

Emmett-Oglesby, M.; Mathis, D. Chronic administration of SCH 23390 produces sensitization to the discriminative stimulus properties of cocaine. In: Harris, LS., editor. Problems of drug dependence; Proceedings of the 50th Annual Scientific Meeting, The College on Problems of Drug Dependence; United States Department of Health and Human Services, Rockville, MD. 1988; p. 367

Ettenberg A, Pettit HO, Bloom FE, Koob GF. Heroin and cocaine intravenous self-administration in rats: mediation by separate neural systems. Psychopharmacology 1982;78:204–209. [PubMed: 6296898]

Everitt BJ, Robbins TW. Second-order schedules of drug reinforcement in rats and monkeys: measurement of reinforcing efficacy and drug-seeking behaviour. Psychopharmacology 2000;153:17–30. [PubMed: 11255926]

Feltenstein MW, Altar CA, See RE. Aripiprazole blocks reinstatement of cocaine seeking in an animal model of relapse. Biol Psychiatry 2007;61:582–590. [PubMed: 16806092]

Ferraro L, Antonelli T, Tanganelli S, O'Connor WT, Perez de la Mora M, Mendez-Franco J, Rambert FA, Fuxe K. The vigilance promoting drug modafinil increases extracellular glutamate levels in the medial preoptic area and the posterior hypothalamus of the conscious rat: prevention by local GABAA receptor blockade. Neuropsychopharmacology 1999;20:346–356. [PubMed: 10088135]

Fischman MW, Johanson CE. Ethical and practical issues involved in behavioral pharmacology research that administers drugs of abuse to human volunteers. Behav Pharmacol 1998;9:479–498. [PubMed: 9862072]

Fischman MW, Schuster CR, Renekov L, Shick JF, Krasnegor NA, Fennell W, Freedman DX. Cardiovascular and subjective effects of intravenous cocaine administration in humans. Arch Gen Psychiatry 1976;33:983–989. [PubMed: 949232]

Fischman MW, Foltin RW, Nestadt G, Pearlson GD. Effects of desipramine maintenance on cocaine self-administration by humans. J Pharmacol Exp Ther 1990;253:760–770. [PubMed: 2338656]

Foltin RW, Fischman MW. Smoked and intravenous cocaine in humans: acute tolerance, cardiovascular and subjective effects. J Pharmacol Exp Ther 1991;257:247–261. [PubMed: 2019989]

Foltin RW, Fischman MW. Self-administration of cocaine by humans: choice between smoked and intravenous cocaine. J Pharmacol Exp Ther 1992;261:841–849. [PubMed: 1602388]

Foltin RW, Fischman MW. Effects of buprenorphine on the self-administration of cocaine by humans. Behav Pharmacol 1994;5:79–89. [PubMed: 11224254]

Foltin RW, Fischman MW. Effects of methadone or buprenorphine maintenance on the subjective and reinforcing effects of intravenous cocaine in humans. J Pharmacol Exp Ther 1996;278:153–164.

Foltin RW, Haney M. Intranasal cocaine in humans: acute tolerance, cardiovascular and subjective effects. Pharmacol Biochem Behav 2004;78:93–101. [PubMed: 15159138]

Foltin RW, Ward AS, Collins ED, Haney M, Hart CL, Fischman MW. The effects of venlafaxine on the subjective, reinforcing, and cardiovascular effects of cocaine in opioid-dependent and non-opioid-dependent humans. Exp Clin Psychopharmacol 2003;11:123–130. [PubMed: 12755456]

Gonzalez G, Oliveto A, Kosten TF. Treatment of heroin (diamorphine) addiction: current approaches and future prospects. Drugs 2002;62:1331–1343. [PubMed: 12076182]

Gorelick DA, Wilkins JN. Bromocriptine treatment for cocaine addiction: association with plasma prolactin levels. Drug Alcohol Depend 2006;81:189–195. [PubMed: 16051446]

Grabowski J, Rhoades H, Silverman P, Schmitz JM, Stotts A, Creson D, Bailey R. Risperidone for the treatment of cocaine dependence: randomized, double-blind trial. J Clin Psychopharmcol 2000;20:305–310.

Grabowski J, Shearer J, Merrill J, Negus SS. Agonist-like, replacement pharmacotherapy for stimulant abuse and dependence. Addict Behav 2004;29:1439–1464. [PubMed: 15345275]

Grassi MC, Cioce AM, Giudici FD, Antonilli L, Nencini P. Short-term efficacy of disulfiram or naltrexone in reducing positive urinalysis for both cocaine and cocaethylene in cocaine abusers: a pilot study. Pharmacol Res 2007;55:117–121. [PubMed: 17174102]

Greenwald M, Johanson CE, Bueller J, Chang Y, Moody DE, Kilbourn M, Koeppe R, Zubieta JK. Buprenorphine duration of action: mu-opioid receptor availability and pharmacokinetic and behavioral indices. Biol Psychiatry 2007;61:101–110. [PubMed: 16950210]

Griffiths RR, Wurster RM, Brady JV. Discrete-trial choice procedure: effects of naloxone and methadone on choice between food and heroin. Pharmacol Rev 1976;27:357–65. [PubMed: 817307]

Gui-Hua C, Perry BD, Woolverton WL. Effects of chronic SCH 23390 or acute EEDQ on the discriminative stimulus effects of SKF 38393. Pharmacol Biochem Behav 1992;41:321–327. [PubMed: 1349436]

Haney M, Kosten TR. Therapeutic vaccines for substance dependence. Drug Discov Today 2005;2:65–69.

Haney M, Foltin RW, Fischman MW. Effects of pergolide on intravenous cocaine self-administration in men and women. Psychopharmacology 1998;137:15–24. [PubMed: 9631952]

Haney M, Collins ED, Ward AS, Foltin RW, Fischman MW. Effect of a selective dopamine D1 agonist (ABT-431) on smoked cocaine self-administration in humans. Psychopharmacology 1999;143:102–110. [PubMed: 10227086]

Haney M, Ward AS, Foltin RW, Fischman MW. Effects of ecopipam, a selective dopamine D1 antagonist, on smoked cocaine self-administration by humans. Psychopharmacology 2001;155:330–337. [PubMed: 11441422]

Haney M, Hart CL, Foltin RW. Effects of baclofen on cocaine self-administration: opioid- and nonopioid-dependent volunteers. Neuropsychopharmacology 2006;31:1814–1821. [PubMed: 16407903]

Harrigan SE, Downs DA. Continuous intravenous naltrexone effects on morphine self-administration in rhesus monkeys. J Pharmacol Exp Ther 1978;204:481–486. [PubMed: 413904]

Harrington, SE.; Downs, DA. Pharmacological evaluation of narcotic antagonist delivery systems in rhesus monkeys. In: Willette, RE.; Burnett, G., editors. Naltrexone, NIDA Research Monograph 28. 1981. p. 77-100.

Hart CL, Ward AS, Collins ED, Haney M, Foltin RW. Gabapentin maintenance decreases smoked cocaine-related subjective effects, but not self-administration by humans. Drug Alcohol Depend 2004;73:279–287. [PubMed: 15036550]

Hart CL, Haney M, Collins ED, Rubin E, Foltin RW. Smoked cocaine self-administration by humans is not reduced by large gabapentin maintenance doses. Drug Alcohol Depend 2007a;86:274–277. [PubMed: 16879931]

Hart CL, Haney M, Vosburg SK, Rubin E, Foltin RW. Gabapentin does not reduce smoked cocaine self-administration: employment of a novel self-administration procedure. Behav Pharmacol 2007b; 18:71–75. [PubMed: 17218799]

Hart CL, Haney M, Vosburg SK, Rubin E, Foltin RW. Human smoked cocaine self-administration is decreased by modafinil. Neuropsychopharmacology. 2008in press

Hatsukami DK, Pentel PR, Glass J, Nelson R, Brauer LH, Crosby R, Hanson K. Methodological issues in the administration of multiple doses of smoked cocaine-base in humans. Pharmacol Biochem Behav 1994;47:531–540. [PubMed: 8208771]

Hess EJ, Albers LJ, Le H, Creese I. Effects of chronic SCH23390 treatment on the biochemical and behavioral properties of D1 and D2 dopamine receptors: potentiated behavioral responses to a D2 dopamine agonist after selective D1 dopamine receptor upregulation. J Pharmacol Exp Ther 1986;238:846–854. [PubMed: 3018223]

Higgins ST, Bickel WK, Hughes JR. Influence of an alternative reinforcer on human cocaine self-administration. Life Sci 1994;55:179–187. [PubMed: 8007760]

Howell LL, Byrd LD. Characterization of the effects of cocaine and GBR 12909, a dopamine uptake inhibitor, on behavior in the squirrel monkey. J Pharmacol Exp Ther 1991;258:178–185. [PubMed: 1677037]

Hubner CB, Moreton JE. Effects of selective D1 and D2 dopamine antagonists on cocaine self-administration in the rat. Psychopharmacology 1991;105:151–156. [PubMed: 1839063]

Jackson DM, Westlind-Danielsson A. Dopamine receptors: molecular biology, biochemistry and behavioural aspects. Pharmacol Ther 1994;64:291–370. [PubMed: 7878079]

Jasinski DR. An evaluation of the abuse potential of modafinil using methylphenidate as a reference. J Psychopharmacol 2000;14:53–60. [PubMed: 10757254]

Jasinksi DR, Pervnick JS, Griffith JD. Human pharmacology and abuse potential of the analgesic buprenorphine. Arch Gen Psychiatry 1978;35:601–616.

Johanson CE, Balster RL. A summary of the results of a drug self-administration study using substitution procedures in rhesus monkeys. Bull Narc 1978;30:43–54. [PubMed: 36945]

Johnson RE, Chutuape MA, Strain EC, Walksh SL, Stitzer ML, Bigelow GE. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. N Engl J Med 2000;343:1290–1297. [PubMed: 11058673]

Jones BE, Prada JA. Drug-seeking behavior during methadone maintenance. Psychopharmacologia 1975;41:7–10. [PubMed: 47638]

Jones BE, Prada JA. Effects of methadone and morphine on drugseeking behavior in the dog. Psychopharmacologia 1977;54:109–112.

Kampman KM, Dackis C, Lynch KG, Pettinati H, Tirado C, Gariti P, Sparkman T, Atzram M, O'Brien CP. A double-blind, placebo-controlled trial of amantadine, propranolol, and their combination for the treatment of cocaine dependence in patients with severe cocaine withdrawal symptoms. Drug Alcohol Depend 2006;85:129–137. [PubMed: 16697124]

Kantak KM. Vaccines against drugs of abuse: a viable treatment option? Drugs 2003;63:341–352. [PubMed: 12558457]

Kebabian JW, Calne DB. Multiple receptors for dopamine. Nature 1979;277:93–96. [PubMed: 215920]

Kleber HD. Naltrexone. J Subst Abuse Treat 1985;2:117–112. [PubMed: 3007777]

Kleven MS, Woolverton WL. Effects of continuous infusions of SCH 23390 on cocaine- or food-maintained behavior in rhesus monkeys. Behav Pharmacol 1990;1:365–373. [PubMed: 11175421]

Koob GF, Pettit HO, Ettenberg A, Bloom FE. Effects of opiate antagonists and their quaternary derivatives on heroin self-administration in the rat. J Pharmacol Exp Ther 1984;229:481–486. [PubMed: 6716270]

Korotkova TM, Klyuch BP, Ponomarenko AA, Lin JS, Haas HL, Sergeeva OA. Modafinil inhibits rat midbrain dopaminergic neurons through D2-like receptors. Neuropharmacology 2007;52:626–633. [PubMed: 17070873]

Kosten TA. Enhanced neurobehavioral effects of cocaine with chronic neuroleptic exposure in rats. Schizophr Bull 1997;23:203–213. [PubMed: 9165631]

Kosten TA, DeCaprio JL, Nestler EJ. Long-term haloperidol administration enhances and short-term administration attenuates the behavioral effects of cocaine in a place conditioning procedure. Psychopharmacology 1996;128:304–312. [PubMed: 8972550]

Kosten TR, Rosen M, Bond J, Settles M, Roberts JS, Shields J, Jack L, Fox B. Human therapeutic cocaine vaccine: safety and immunogenicity. Vaccine 2002;20:1196–1204. [PubMed: 11803082]

Lile JA, Nader MA. The abuse liability and therapeutic potential of drugs evaluated for cocaine addiction as predicted by animal models. Current Neuropharmacology 2003;1:21–46.

Lile JA, Stoops WW, Vansickel AR, Glaser PEA, Hays LR, Rush CR. Aripiprazole attenuates the discriminative-stimulus and subject-rated effects of d-amphetamine in humans. Neuropsychopharmacology 2005;30:2103–2114. [PubMed: 15988473]

Lukas SE, Brady JV, Griffiths RR. Comparison of opioid self-injection and disruption of schedule-controlled performance in the baboon. J Pharmacol Exp Ther 1986;238:924–931. [PubMed: 3746670]

Madras BK, Fahey MA, Bergman J, Canfield DR, Spealman RD. Effects of cocaine and related drugs in nonhuman primates. I. [3H] cocaine binding sites in caudate-putamen. J Pharmacol Exp Ther 1989;251:131–141. [PubMed: 2529364]

Madras BK, Xie Z, Lin Z, Jassen A, Panas H, Lynch L, Johnson R, Livni E, Spencer TJ, Bonab AA, Miller GM, Fischman AJ. Modafinil occupies dopamine and norepinephrine transporters in vivo and modulates the transporters and trace amine activity in vitro. J Pharmacol Exp Ther 2006;319:561–569. [PubMed: 16885432]

Malcolm R, Kajdasz DK, Herron J, Anton RF, Brady KT. A double-blind, placebo-controlled outpatient trial of pergolide for cocaine dependence. Drug Alcohol Depend 2000;60:161–168. [PubMed: 10940543]

Malcolm R, Swayngim K, Donovan JL, DeVane CL, Elkashef A, Chiang N, Khan R, Mojsiak J, Myrick DL, Hedden S, Cochran K, Woolson RF. Modafinil and cocaine interactions. Am J Drug Alcohol Abuse 2006;32:577–587. [PubMed: 17127546]

Marlatt GA. Models of relapse and relapse prevention: a commentary. Exp Clin Psychopharmacol 1996;4:55–60.

Marsch LA, Bickel WK, Badger GJ, Jacobs EA. Buprenorphine treatment for opioid dependence: the relative efficacy of daily, twice and thrice weekly dosing. Drug Alcohol Depend 2005;77:195–204. [PubMed: 15664721]

Martell BA, Mitchell E, Poling J, Gonsai K, Kosten TR. Vaccine pharmacotherapy for the treatment of cocaine dependence. Biol Psychiatry 2005;58:158–164. [PubMed: 16038686]

McCance-Katz E, Kosten TA, Kosten TR. Going from the bedside back to the bench with ecopipam: a new strategy for cocaine pharmacotherapy development. Psychopharmacology 2001;155:327–329. [PubMed: 11441421]

McGregor A, Roberts DCS. Dopaminergic antagonism within the nucleus accumbens or the amygdala produces differential effects on intravenous cocaine self-administration under fixed and progressive ratio schedules of reinforcement. Brain Res 1993;624:245–252. [PubMed: 8252397]

Mello NK, Mendelson JH. Buprenorphine suppresses heroin use by heroin addicts. Science 1980;207:657–659. [PubMed: 7352279]

Mello NK, Mendelson JH. Behavioral pharmacology of buprenorphine. Drug Alcohol Depend 1985;14:283–303. [PubMed: 3888577]

Mello MK, Negus SS. Preclinical evaluation of pharmocotherapies for treatment of cocaine and opioid abuse using drug self-administration procedures. Neuropsychopharmacology 1996;14:375–424. [PubMed: 8726752]

Mello NK, Negus SS. The effects of buprenorphine on self-administration of cocaine and heroin "speedball" combinations and heroin alone by rhesus monkeys. J Pharmacol Exp Ther 1998;285:444–456. [PubMed: 9580582]

Mello NK, Mendelson JH, Kuehnle JC, Sellers MS. Operant analysis of human heroin self-administration and the effects of naltrexone. J Pharmacol Exp Ther 1981a;216:45–54. [PubMed: 7452507]

Mello NK, Bree MP, Mendelson JH. Buprenorphine self-administration by rhesus monkey. Pharmacol Biochem Behav 1981b;15:215–225. [PubMed: 7198266]

Mello NK, Mendelson JH, Kuehnle JC. Buprenorphine effects on human heroin self-administration: an operant analysis. J Pharmacol Exp Ther 1982;223:30–39. [PubMed: 7120124]

Mello NK, Bree MP, Mendelson JH. Comparison of buprenorphine and methadone effects on opiate self-administration in primates. J Pharmacol Exp Ther 1983;225:378–386. [PubMed: 6188822]

Mello NK, Lukas SE, Bree MP, Mendelson JH. Progressive ratio performance maintained by buprenorphine, heroin and methadone in Macaque monkeys. Drug Alcohol Depend 1988;21:81–97. [PubMed: 3416736]

Meyer, RE.; Mirin, SM. The heroin stimulus: implication for a theory of addiction. Plenum; New York: 1979.

Mignot E, Nishino S, Guilleminault C, Dement WC. Modafinil binds to the dopamine uptake carrier site with low affinity. Sleep 1994;17:436–437. [PubMed: 7991954]

Myrick H, Malcolm R, Taylor B, LaRowe S. Modafinil: preclinical, clinical, and post-marketing surveillance—a review of abuse liability issues. Ann Clin Psychiatry 2004;16:101–109. [PubMed: 15328903]

Nader MA, Woolverton WL. Effects of increasing the magnitude of an alternative reinforcer on drug choice in a discrete-trials choice procedure. Psychopharmacology 1992;105:169–174. [PubMed: 1796123]

Nann-Vernotica E, Donny EC, Bigelow GE, Walsh SL. Repeated administration of the D1/5 antagonist ecopipam fails to attenuate the subjective effects of cocaine. Psychopharmacology 2001;155:338–347. [PubMed: 11441423]

Negus SS. Choice between heroin and food in nondependent and heroin-dependent rhesus monkeys: effects of naloxone, buprenorphine, and methadone. J Pharmacol Exp Ther 2006;317:711–723. [PubMed: 16456085]

Negus SS, Mello NK. Effects of chronic d-amphetamine treatment on cocaine and food-maintained responding under a second-order schedule in rhesus monkeys. Drug Alcohol Depend 2003;70:39–52. [PubMed: 12681524]

Newton TF, Kalechstein A, Beckson M, Bartzokis G, Bridge TP, Ling W. Effects of selegiline pretreatment on response to experimental cocaine administration. Psychiatry Res 1999;87:101–106. [PubMed: 10579543]

Obadia Y, Perrin V, Feroni I, Vlahov D, Moatti J-P. Injecting misuse of buprenorphine among French drug users. Addiction 2001;96:267–272. [PubMed: 11182872]

O'Brien CP, Greenstein RA, Mintz J, Woody GE. Clinical experience with naltrexone. Am J Drug Alcohol Abuse 1975;2:365–377. [PubMed: 1227298]

Pickens R. Self-administration of stimulants by rats. Int J Addict 1968;3:215–221.

Platt DM, Rowlett JK, Spealman RD. Modulation of cocaine and food self-administration by low- and high-efficacy D1 agonists in squirrel monkeys. Psychopharmacology 2001;157:208–216. [PubMed: 11594448]

Platt DM, Rowlett JK, Spealman RD. Behavioral effects of cocaine and dopaminergic strategies for preclinical medication development. Psychopharmacology 2002;163:265–282. [PubMed: 12373428]

Preston KL, Sullivan JT, Strain EC, Bigelow GE. Effects of cocaine alone and in combination with bromocriptine in human cocaine abusers. J Pharmacol Exp Ther 1992;262:279–291. [PubMed: 1625204]

Pulvirenti L, Balducci C, Piercy M, Koob GF. Characterization of the effects of the partial dopamine agonist terguride on cocaine self-administration in the rat. J Pharmacol Exp Ther 1998;286:1231–1238. [PubMed: 9732383]

Richardson NR, Roberts DC. Progressive ratio schedules in drug self-administration studies in rats: a method to evaluate reinforcing efficacy. J Neurosci Methods 1996;66:1–11. [PubMed: 8794935]

Ritz MC, Lamb RJ, Goldberg SR, Kuhar MJ. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. Science (Washington, DC) 1987;237:1219–1223.

Romach MK, Flue P, Kampman K, Kaplan HL, Somer GR, Poole S, Clarke L, Coffin V, Cornish J, O'Brien CP, Sellers EM. Attenuation of the euphoric effects of cocaine by the dopamine D1/D5 antagonist ecopipam (SCH 39166). Arch Gen Psychiatry 1999;56:1101–1106. [PubMed: 10591286]

Rowlett JK, Wilcox KM, Woolverton WL. Self-administration of cocaine-heroin combinations by rhesus monkeys: antagonism by naltrexone. J Pharmacol Exp Ther 1998;286:61–69. [PubMed: 9655842]

Rush CR, Kelly TH, Hays LR, Baker RW, Wooten AF. Acute behavioral and physiological effects of modafinil in drug abusers. Behav Pharmacol 2002a;13:105–115. [PubMed: 11981223]

Rush CR, Kelly TH, Hays LR, Wooten AF. Discriminative-stimulus effects of modafinil in cocaine-trained humans. Drug Alcohol Depend 2002b;67:311–322. [PubMed: 12127202]

Schecter A. The role of narcotic antagonists in the rehabilitation of opiate addicts: a review of naltrexone. Am J Drug Alcohol Abuse 1980;7:1–18. [PubMed: 6254356]

Schindler CW, Panlilio LV, Goldberg SR. Second-order schedules of drug self-administration in animals. Psychopharmacology 2002;63:327–344. [PubMed: 12373434]

Schuster, CR.; Johanson, CE. The use of animal models for the study of drug abuse. In: Gibbins, RJ.; Israel, Y.; Kalant, H.; Popham, R.; Schmidt, W.; Smart, RG., editors. Research advances in alcohol and drug problems. Vol. 1. Wiley; New York: 1974. p. 1-31.

Shoptaw S, Yang X, Rotheram-Fuller EJ, Hsieh YC, Kintaudi PC, Charuvastra VC, Ling W. Randomized placebo-controlled trial of baclofen for cocaine dependence: preliminary effects for individuals with chronic patterns of cocaine use. J Clin Psychiatry 2003;64:1440–1448. [PubMed: 14728105]

Sofuoglu M, Pentel PR, Bliss RL, Goldman AI, Hatsukami DK. Effects of phenytoin on cocaine self-administration in humans. Drug Alcohol Depend 1999;53:273–275. [PubMed: 10080053]

Sofuoglu M, Singha A, Kosten TR, McCance-Katz FE, Petrakis I, Oliveto A. Effects of naltrexone and isradipine, alone or in combination, on cocaine responses in humans. Pharmacol Biochem Behav 2003;75:801–808. [PubMed: 12957222]

Spealman RD, Goldberg SR. Drug self-administration by laboratory animals: control by schedules of reinforcement. Annu Rev Pharmacol Toxicol 1978;8:313–339. [PubMed: 348062]

Spealman RD, Bergman J, Madras BK, Kamien JB, Melia KF. Role of D1 and D2 dopamine receptors in the behavioral effects of cocaine. Neurochem Int 1992;20:147S–152S. [PubMed: 1365414]

Spealman RD, Barrett-Larimore RL, Rowlett JK, Platt DM, Khroyan TV. Pharmacological and environmental determinants of relapse to cocaine-seeking behavior. Pharmacol Biochem Behav 1999;64:327–336. [PubMed: 10515309]

Spragg SD. Morphine addiction in chimpanzees. Comparative Psychology Monographs 1940;15:1–132.

Stafford D, LeSage MG, Glowa JR. Progressive-ratio schedules of drug delivery in the analysis of drug self-administration: a review. Psychopharmacology 1998;139:169–184. [PubMed: 9784071]

Stoops WW, Lile JA, Fillmore MT, Glaser PE, Rush CR. Reinforcing effects of modafinil: influence of dose and behavioral demands following drug administration. Psychopharmacology 2005;182:186–193. [PubMed: 15986191]

Strain EC, Bigelow GE, Liebson IA, Stitzer ML. Moderate- vs high-dose methadone in the treatment of opioid dependence: a randomized trial. JAMA 1999;281:1000–1005. [PubMed: 10086434]

Sullivan MA, Vosburg SK, Comer SD. Depot naltrexone: antagonism of the reinforcing, subjective and physiological effects of heroin. Psychopharmacology 2006;189:37–46. [PubMed: 16972105]

Thompson T, Schuster CR. Morphine self-administration, food reinforced, and avoidance behaviors in rhesus monkeys. Psychopharmacology 1964;5:87–94.

Tiihonen J, Kuoppasalmi K, Föhr J, Tuomola P, Kuikanmäki O, Vorma H, Sokero P, Haukka J, Meririnne E. A comparison of aripiprazole, methylphenidate, and placebo for amphetamine dependence. Am J Psychiatry 2007;164:160–162. [PubMed: 17202560]

Vaccheri A, Dall'Olio R, Gandolfi O, Roncada P, Montanaro N. Enhanced stereotyped response to apomorphine after chronic D-1 blockade with SCH 23390. Psychopharmacology 1987;91:394–396. [PubMed: 2882541]

Vidal-Trecan G, Verscon I, Nabet N, Boissonnas A. Intravenous use of prescribed sublingual buprenorphine tablets by drug users receiving maintenance therapy in France. Drug Alcohol Depend 2003;69:175–181. [PubMed: 12609698]

Walsh SL, Eissenberg T. The clinical pharmacology of buprenorphine: extrapolating from the laboratory to the clinic. Drug Alcohol Depend 2003;70:S13–S27. [PubMed: 12738347]

Walsh SL, Geter Douglas B, Strain EC, Bigelow GE. Enadoline and butorphanol: evaluation of k-agonists on cocaine pharmacodynamics and cocaine self-administration in humans. J Pharmacol Exp Ther 2001;299:147–158. [PubMed: 11561074]

Weeks JR. Experimental morphine addiction: method for automatic intravenous injection in unrestrained rats. Science 1962;138:143–144. [PubMed: 14005543]

Weeks JR, Collins RJ. Changes in morphine self-administration in rats induced by prostaglandin E1 and naloxone. Prostaglandins 1976;12:11–19. [PubMed: 986671]

Weerts EM, Fantegrossi WE, Goodwin AK. The value of nonhuman primates in drug abuse research. Exp Clin Psychopharmacol 2007;15:309–327. [PubMed: 17696678]

White FJ, Joshi A, Koeltzow TE, Hu XT. Dopamine receptor antagonists fail to prevent induction of cocaine sensitization. Neuropsychopharmacology 1998;18:26–40. [PubMed: 9408916]

Winger G. Dopamine antagonist effects on behavior maintained by cocaine and alfentanil in rhesus monkeys. Behav Pharmacol 1994;5:141–152. [PubMed: 11224262]

Winger G, Woods JH. Effects of buprenorphine on behaviour maintained by heroin and alfentanil in rhesus monkeys. Behav Pharmacol 1996;7:155–159. [PubMed: 11224407]

Winger G, Woods JH. The effects of chronic morphine on behavior reinforced by several opioids or by cocaine in rhesus monkeys. Drug Alcohol Depend 2001;62:181–189. [PubMed: 11295322]

Winger G, Skjoldager P, Woods JH. Effects of buprenorphine and other opioid agonists and antagonists on alfentanil- and cocaine-reinforced responding in rhesus monkeys. J Pharmacol Exp Ther 1992;261:311–317. [PubMed: 1560376]

Woods JH, Schuster CR. Reinforcement properties of morphine, cocaine and SPA as a function of unit dose. Internat J Addict 1968;3:231–237.

Woolverton WL. Effects of a D1 and a D2 dopamine antagonist on the self-administration of cocaine and piribedil by rhesus monkeys. Pharmacol Biochem Behav 1986;24:531–535. [PubMed: 2871561]

Woolverton WL, Anderson KG. Effects of delay to reinforcement on the choice between cocaine and food in rhesus monkeys. Psychopharmacology 2006;186:99–106. [PubMed: 16568283]

Woolverton WL, Balster RL. Effects of antipsychotic compounds in rhesus monkeys given a choice between cocaine and food. Drug Alcohol Depend 1981;8:69–78. [PubMed: 7297414]

Woolverton WL, Johnson KM. Neurobiology of cocaine abuse. Trends Pharmacol Sci 1992;13:193–200. [PubMed: 1604712]

Woolverton WL, Virus RM. The effects of a D1 and a D2 dopamine antagonist on behavior maintained by cocaine or food. Pharmacol Biochem Behav 1989;32:691–697. [PubMed: 2662223]

Woolverton WL, English JA, Weed MR. Choice between cocaine and food in a discrete-trials procedure in monkeys: a unit price analysis. Psychopharmacology 1997;133:269–274. [PubMed: 9361333]

Young AM, Stephens KR, Hein DW, Woods JH. Reinforcing and discriminative stimulus properties of mixed agonist-antagonist opioids. J Pharmacol Exp Ther 1984;229:118–126. [PubMed: 6142942]