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Investigating the Pharmacological and Nonpharmacological Factors That Modulate Drug Reinforcement

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Drug use is driven by principles of reinforcement and is sensitive to influences in the environmental context in which it occurs. Although a wide range of factors has been shown to directly influence the reinforcing effects of commonly abused drugs, 2 general types include pharmacological and nonpharmacological factors. Both can assert a powerful impact on a drug's reinforcing effects and, therefore, the degree to which a particular drug comes to be used and abused. This invited review seeks to briefly describe some of the current psychopharmacology research on the interactions between these factors and drug abuse. Several pharmacological influences on drug use will be discussed, including the interactions between psychomotor stimulants and recent advances in the development of pharmacotherapies for opioid abuse. With regard to nonpharmacological factors, there is a large body of research demonstrating that nondrug reinforcers can exert a powerful influence on the reinforcing effects of commonly abused drugs. More specifically, identifying alternative nondrug sources of reinforcement can, if made available contingent on drug abstinence, produce robust decreases in drug self-administration. Presented here is a very brief review of some recent scientific efforts to develop and extend behavioral interventions targeting drug use across a wide range of clinical populations. In summary, understanding the interactions among the variables present in the context of drug use is critical to understanding risk factors for substance use disorders as well as developing efficacious treatments for drug dependence.

Keywords: reinforcement, drug abuse, pharmacotherapy, contingency management

Over the past several decades, an extensive body of research has demonstrated that reinforcement processes play a central role in the initiation, maintenance, and cessation of drug self-administration. This research provided experimental evidence that abused drugs promote repeated use by functioning as unconditioned positive reinforcers much in the same way as the natural reinforcers of food, water, and sex. It demonstrated drug self-administration to be orderly behavior, subject to the laws of learning and conditioning, and showed the extent to which drug use is influenced by the environmental context in which it occurs. This knowledge placed drug use within a body of scientific knowledge whose principles could be used to directly modulate rates of drug use and to develop new and effective treatments (Higgins, Heil, & Lussier, 2004).

Although a wide range of factors has been shown to modulate the reinforcing effects of commonly abused drugs, the majority of my work thus far has centered around two general types: pharmacological and nonpharmacological. Drug use, and more specifically the extent to which a drug serves as a reinforcer, can be exquisitely sensitive to both of these influences. Indeed, understanding the interactions between a drug and the pharmacological and nonpharmacological variables present in the context of drug use can be critical to understanding risk factors for substance use disorders as well as developing efficacious treatments for drug dependence. In terms of the potential pharmacological factors that may influence a drug's reinforcing effects, I have primarily focused on two areas. First, I have been interested in examining the pharmacological interactions between psychomotor stimulants. The second area of my research has focused on opioid pharmacotherapies that attenuate the reinforcing effects of exogenously administered opioids. With

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regard to nonpharmacological factors, there is a large body of research demonstrating that nondrug reinforcers in the environment can exert a powerful influence on the reinforcing effects of commonly abused drugs. On the basis of the above reinforcement principles that guide a behavioral understanding of drug abuse and dependence, there is a strong rationale for identifying nondrug sources of reinforcement that, if made available contingent on drug abstinence, can produce robust decreases in drug self-administration. Toward this end, I have focused much of my scientific efforts on developing and testing behavioral interventions to reduce drug use across a wide range of clinical populations. Although my work thus far examining both pharmacological and nonpharmacological influences on drug reinforcement has spanned a wide range of settings (e.g., laboratory and clinic), drug classes, and clinical populations, I have generally aimed to follow one overarching theme: to advance an understanding of the factors that influence the reinforcing effects of commonly abused drugs.

Modulating Drug Reinforcement Using Pharmacological Factors

Stimulant Pretreatment Increases the Reinforcing Effects of Cigarette Smoking

One potential influence on a drug's reinforcing efficacy is concurrent use of other drugs. Psychomotor stimulants, such as *d*-amphetamine and cocaine, have been reliably demonstrated to increase cigarette smoking (Chait & Griffiths, 1983; Cousins, Stamat, & de Wit, 2001; Henningfield, Clayton, & Pollin, 1990; Henningfield & Griffiths, 1981; Higgins et al., 1994; Mello & Mendelson, 1986; Nemeth-Coslett, Henningfield, Katz, & Goldberg, 1986; Roll, Higgins, & Tidey, 1997; Schuster, Lucchesi, & Emley, 1979). The ability of stimulants to increase smoking can have serious health implications, including increased risk for cardiovascular disease, pulmonary disease, and cancer (Benowitz, 1998; Minor, Scott, Brown, & Winniford, 1991; Moliterno et al., 1994). This interaction also is of concern considering the widespread use of stimulant medications to treat attention-deficit/hyperactivity disorder among adolescents. Stimulants, such as methylphenidate and *d*-amphetamine, are the most commonly prescribed medications used in the treatment of attention-deficit/hyperactivity disorder (Biederman, Wilen, Mick, Spencer, & Faraone, 1999; Challman & Lipsky, 2000; Zito et al., 2000). Indeed, a recent study has provided empirical support for methylphenidate's ability to increase smoking (Rush et al., 2005). If psychomotor stimulants increase the reinforcing effects of cigarette smoking, even among a subset of users, it is a reasonable expectation that at least some children and adolescents receiving these medications may be at greater risk for initiating smoking or, following some experimental use, becoming regular smokers.

The possible mechanisms involved in such drug-produced changes in smoking are not well understood. My research group has been interested in two possible explanations for the ability of psychomotor stimulants to increase smoking, and it was this line of research that I became involved with during my graduate studies at the University of Vermont. First, there may be a unique pharmacological interaction whereby ingestion of a stimulant increases the reinforcing effects of smoking, perhaps by increasing the reinforcing effects of nicotine. There is a robust literature supporting an important role for the reinforcing effects of nicotine in maintaining smoking (Henningfield, 1984; National Institute of Drug Abuse, 2001). Second, stimulants may increase smoking as part of a general increase in activity rather than any specific effect on cigarette smoking per se. That is, stimulants and a wide range of other abused drugs can increase rates of operant responding without altering the efficacy of the reinforcer maintaining responding (Kelleher & Morse, 1968). Whether this is the case with smoking or these drugs specifically increase the reinforcing effects of smoking has remained unclear.

In an initial study on this question, my colleagues and I examined whether *d*-amphetamine (0, 7.5, or 15 mg/70.0 kg) increased preference for cigarette smoking over monetary reinforcement in a discrete-trial choice procedure (Tidey, O'Neill, & Higgins, 2000). Such preference changes in concurrent choice procedures are commonly used as an index of changes in the relative reinforcing effects of a consequence (de Villiers, 1977; Mazur, 1994). In that study, *d*-amphetamine increased preference for smoking over money, suggesting that *d*-amphetamine, and perhaps other stimulants, increase the relative reinforcing effects of smoking specifically rather than just increasing smoking as part of a general increase in activity.

In a subsequent study, my colleagues and I used a progressive-ratio schedule as another method to examine the effects of *d*-amphetamine on the reinforcing effects of cigarette smoking (Sigmon, Tidey, Badger, & Higgins, 2003). In progressive-ratio arrangements, the response requirement for obtaining each reinforcer increases following the delivery of the previous reinforcer and continues to escalate until responding ceases (Hodos, 1961; Hodos & Kalman, 1963). The final ratio completed, or break point, is considered an index of the strength or efficacy of the reinforcing consequence under study.

Participants were 18 volunteers who smoked approximately 20 cigarettes per day. A progressive-ratio schedule was used to examine the acute effects of orally administered *d*-amphetamine (0, 5, 10, 15 mg/70 kg) on the reinforcing effects of smoking (2 puffs/ratio) and money ($1/ratio). *d*-Amphetamine produced a modest, nonsignificant increase in overall break point maintained by cigarette smoking (see Figure 1, top). However, individual participant data revealed systematic differences, with participants separating into two distinct groups with respect to how *d*-amphetamine altered smoking break point. In one group of responders ($n = 10$), *d*-amphetamine significantly increased break point for responding maintained by smoking (see Figure 1, bottom). In the other subgroup of nonresponders ($n = 8$), *d*-amphetamine significantly decreased smoking break point. Overall, these results provide further evidence that

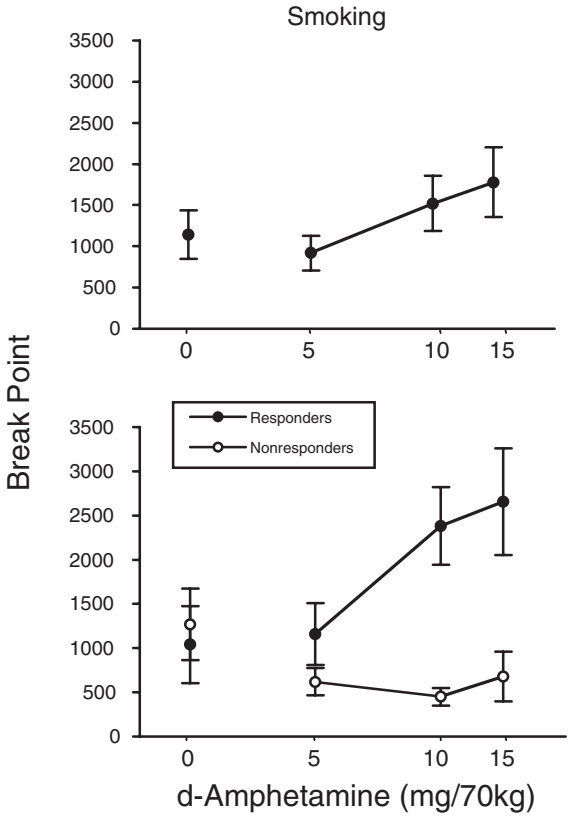


Figure 1. Mean break points as a function of placebo and 5, 10, and 15 mg/70 kg *d*-amphetamine maintained by smoking for all participants as a group (top) and with participants categorized as responders (filled circles) and nonresponders (open circles; bottom). Error bars represent ± *SEM*. From "Acute Effects of *d*-Amphetamine on Progressive-Ratio Performance Maintained by Cigarette Smoking and Money," by S. C. Sigmon, J. W. Tidey, G. J. Badger, and S. T. Higgins, 2003, *Psychopharmacology, 167,* p. 396. Copyright 2003 by Springer Science and Business Media. Reprinted with permission.

stimulants can increase the reinforcing effects of smoking in at least a subset of individuals.

Of note, although responders and nonresponders generally did not differ in baseline demographic characteristics, the individual differences noted in *d*-amphetamine's effects on smoking were associated with differences in participant ratings. Responders reported greater drug effects in general (e.g., increased ratings of "drug effects" and "slurred speech") and also more positive effects (e.g., increased ratings of "feel good effects" and "feel high"). Responders and nonresponders did not differ in their ratings of negative drug effects. Put succinctly, *d*-amphetamine's increasing effects on break point maintained by smoking were associated with a more positive profile and perhaps a somewhat greater sensitivity overall to drug effects. Future research efforts will be important to more thoroughly investigate such individual differences in the reinforcing effects of commonly used drugs.

Chronic Nicotine Maintenance Attenuates the Reinforcing and Subjective Effects of Intravenous Nicotine, But Not Cocaine and Caffeine, in Stimulant Abusers

Another way in which pharmacological factors may influence a drug's reinforcing efficacy is through the tolerance that develops following chronic administration. As a postdoctoral fellow at the Behavioral Pharmacology Research Unit at Johns Hopkins University, I had the opportunity to conduct an inpatient laboratory study examining the effects of chronic nicotine maintenance on the acute effects of intravenous (IV) nicotine, cocaine, and caffeine (Sobel, Sigmon, & Griffiths, 2004). Nicotine, cocaine, and caffeine are among the most commonly used and abused psychoactive substances. Although they produce their effects through different receptor sites, there is evidence to suggest that all three produce their stimulant and reinforcing effects through modulation of the dopaminergic system (Di Chiara, 2000; Fredholm, Bättig, Holmén, Nehlig, & Zvartau, 1999; Garrett & Griffiths, 1997; Koob & Nestler, 1997; Zernig, O'Laughlin, & Fibiger, 1997). Interactions between nicotine and cocaine are of interest because epidemiological and experimental studies have shown a strong concordance between tobacco and cocaine abuse (Budney, Higgins, Hughes, & Bickel, 1993; Roll, Higgins, Budney, Bickel, & Badger, 1996; Wiseman & McMillan, 1996). Likewise, interactions between nicotine and caffeine are of interest because of the strong concordance between tobacco and caffeine use (Istvan & Matarazzo, 1984; Swanson, Lee, & Hopp, 1994) as well as preclinical and clinical studies showing that chronic caffeine administration potentiates the stimulant and reinforcing effects of nicotine (Jones & Griffiths, 2003; Tanda & Goldberg, 2000). Finally, the effect of nicotine maintenance on acute nicotine effects is important given that nicotine replacement is a widely used strategy for treatment of cigarette smoking. Although nicotine tolerance has been demonstrated using a variety of methodological approaches, studies have typically used relatively modest nicotine maintenance and challenge doses (Perkins, 2002).

This study used a within-participant, double-blind design to evaluate the subjective, reinforcing, and physiological effects of IV placebo, cocaine (15, 30 mg/70 kg), caffeine (200, 400 mg/70 kg), and nicotine (1, 2 mg/70 kg) during each of two phases: a nicotine maintenance phase (21 mg/day nicotine transdermal patch) and a placebo maintenance phase (transdermal placebo patch). Both cocaine and caffeine generally produced significant elevations in ratings over placebo for a range of subjective effects, and these effects were generally not significantly altered by the nicotine or placebo maintenance phases (see Figure 2). In contrast, IV nicotine effects were robustly affected by the nicotine versus placebo maintenance manipulation. During the placebo maintenance phase, nicotine produced clear dose-dependent effects on seven of the eight scales, with the high dose producing ratings approximately threefold greater than the low dose. These dose effects were attenuated during nicotine maintenance, with the high dose failing to

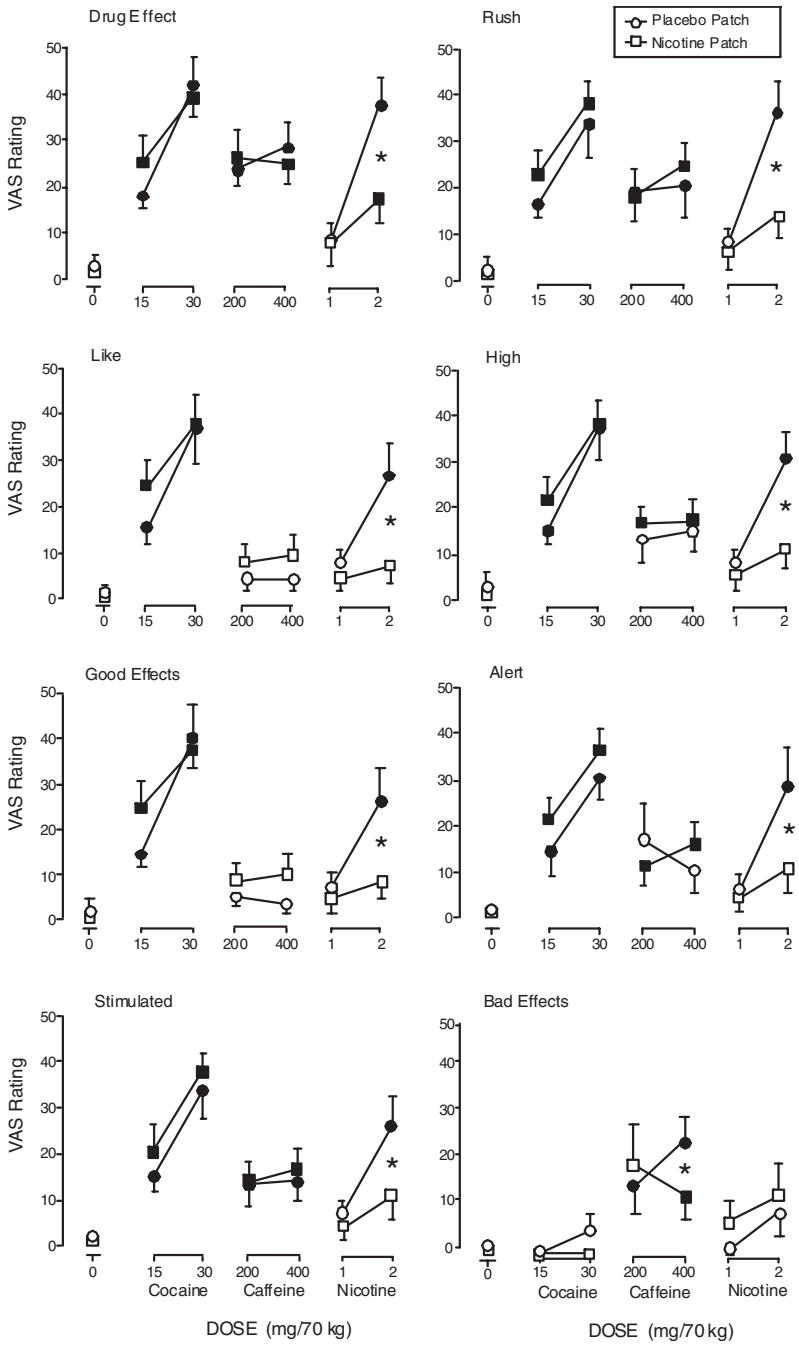


Figure 2. Effects of intravenous placebo, cocaine, caffeine, and nicotine on visual analog scale (VAS) ratings for the placebo maintenance phase (circles) and the nicotine maintenance phase (squares). Data points are means ($n = 9$) of peak change from baseline. Error bars show 1 *SEM*; absence of error bar indicates *SEM* fell within the area of the symbol. Filled symbols indicate mean is significantly different from intravenous placebo ($p \leq .05$). Asterisks indicate a significant difference between the same drug dose in the nicotine maintenance and placebo maintenance phases ($p \leq .05$). From "Nicotine Maintenance Attenuates the Subjective and Reinforcing Effects of Intravenous Nicotine, But Not Cocaine or Caffeine, in Cigarette-Smoking Stimulant Abusers," by B.-F. X. Sobel, S. C. Sigmon, and R. R. Griffiths, 2004, *Neuropsychopharmacology, 29,* p. 996. Copyright 2004 by B.-F. X. Sobel, S. C. Sigmon, and R. R. Griffiths. Reprinted with permission.

produce effects significantly greater than placebo on all measures except drug effect. The finding that nicotine maintenance attenuates the positive and stimulant-like effects of IV nicotine extends prior research showing that tolerance develops to the subjective effects of chronically administered nicotine (Heishman & Henningfield, 2000; Perkins et al., 1993, 1994; West & Russell, 1987).

In order to examine the effects of nicotine maintenance on the reinforcing effects of IV cocaine, caffeine, and nicotine, my colleagues and I used the Drug Versus Money Multiple-Choice Form. This procedure was developed and validated as a tool to efficiently assess drug reinforcement in humans (e.g., Griffiths, Rush, & Puhala, 1996; Griffiths, Troisi, Silverman, & Mumford, 1993; Jones & Griffiths, 2003; Schuh & Griffiths, 1997; Smith, Jones, & Griffiths, 2001). In this study, IV cocaine produced significant dose-related increases in crossover point, which were not significantly affected by nicotine maintenance. IV caffeine and nicotine did not significantly alter crossover points compared with IV placebo. However, as with the subjective ratings, crossover points for IV nicotine were significantly affected by nicotine maintenance. IV nicotine produced modest increases in crossover points during placebo maintenance, whereas it produced modest decreases during nicotine maintenance. Although none of these changes were significantly different from placebo, crossover points for the high dose of nicotine differed significantly between phases (see Figure 3), suggesting that chronic nicotine maintenance may reduce the reinforcing effects of IV nicotine.

In summary, this study provides the most aggressive evaluation of nicotine tolerance to date by testing high IV challenge doses of nicotine and by inducing tolerance with long-term, continuous, double-blind transdermal nicotine administration. The study demonstrates virtually complete tolerance to the subjective effects as well as attenuation of the reinforcing effects of IV nicotine. Further, these results demonstrate that, although chronic nicotine maintenance produces tolerance to the effects of IV nicotine, it does not affect the subjective or reinforcing effects of cocaine or caffeine.

A Novel, Sustained-Release Formulation of Buprenorphine Blocks Opioid Reinforcement

My efforts to evaluate pharmacological factors modulating drug reinforcement have also extended to opioid drugs. While at the Behavioral Pharmacology Research Unit, I had the opportunity to conduct two studies evaluating a novel, sustained-release buprenorphine product. Buprenorphine, an opioid with mixed agonist–antagonist properties, was approved in 2002 for the treatment of opioid dependence in the United States. Clinical studies have demonstrated buprenorphine to be effective in reducing opioid-positive urine specimens and retaining patients in treatment (e.g., Ahmadi, 2002; Bickel et al., 1988b; Johnson, Jaffe, & Fudala, 1992; Kosten & Kleber, 1988; Ling et al., 1998; Lintzeris, Bell, Bammer, Jolley, & Rushworth, 2002; Schottenfeld, Pakes, Oliveto, Ziedonis, & Kosten, 1997; Strain, Stitzer, Liebson, & Bigelow, 1994). Buprenorphine also has a ceiling on its agonist activity that may reduce its abuse liability and contribute to a superior safety profile (Lewis, 1985; Walsh, Preston, Bigelow, & Stitzer, 1995; Walsh, Preston, Stitzer, Cone, & Bigelow, 1994), an ability to attenuate the physiological and subjective effects of other opioid agonists (Bickel et al., 1988a; Jasinski, Pevnick, & Griffith, 1978; Mello, Mendelson, & Kuehnle, 1982; Rosen et al., 1994; Walsh et al., 1995), and a long plasma half-life and long duration of action due to its slow dissociation from the receptor (Bullingham, McQuay, Moore, & Bennett, 1980; Hambrook & Rance, 1976). Finally, the limited withdrawal following discontinuation of buprenorphine treatment may render it appropriate for detoxification treatments (Bickel et al., 1988b; Diamant et al., 1998; Fudala, Jaffe, Dax, & Johnson, 1990; Jasinski et al., 1978; Lintzeris et al., 2002; Mello & Mendelson, 1980; Mello et al., 1982).

A sustained-release or depot formulation of buprenorphine has been developed that could offer several additional advantages over the sublingual forms currently used for opioid treatment. First, it could provide gradual onset and sustained release of buprenorphine that suppresses withdrawal and blocks the effects of exogenously administered opioids for weeks. The gradual release and elimination of buprenorphine also may provide a gradual detoxification with minimal, if any, withdrawal symptoms. Second, a depot formulation might minimize the burdens of patient compliance by requiring less frequent dosing and thereby reducing the frequency of clinic visits and amount of clinical support needed. Finally, depot buprenorphine may reduce risk of illicit diversion by eliminating the need for take-home medication. Taken together, a long-lasting depot form of buprenorphine could offer a promising approach for delivering effective opioid maintenance or detoxification treatment.

In our initial study, my research colleagues and I sought to assess the pharmacokinetics, safety, and patient acceptability of a single dose (58 mg) of depot buprenorphine among opioid-dependent volunteers as well as its time course and efficacy in suppressing opioid withdrawal and blocking opioid effects (Sobel, Sigmon, Walsh, et al., 2004). Participants were 5 opioid-dependent adults. During the first day on the residential unit, they were assessed repeatedly for symptoms of opioid withdrawal and administered oral hydromorphone for suppression of withdrawal. On the second day, participants received the depot buprenorphine injection. Throughout the 6-week study, self-report ratings of opioid withdrawal and agonist effects were collected using a 37-item adjective checklist (Preston, Bigelow, & Liebson, 1988). Observer ratings of opioid withdrawal were made by residential nursing staff using a modified Himmelsbach (1941) withdrawal scale (Eissenberg et al., 1996). Opioid challenge sessions were conducted weekly to examine the ability of depot buprenorphine to block the physiological and subjective effects of a 3-mg hydromorphone challenge injection, which is equivalent to approximately 20–25 mg of parenteral morphine or 10 mg of parenteral heroin and was selected to match the methods of a prior study to allow for a historical comparison (Bigelow, Sobel, Terry, & Liebson, 2001).

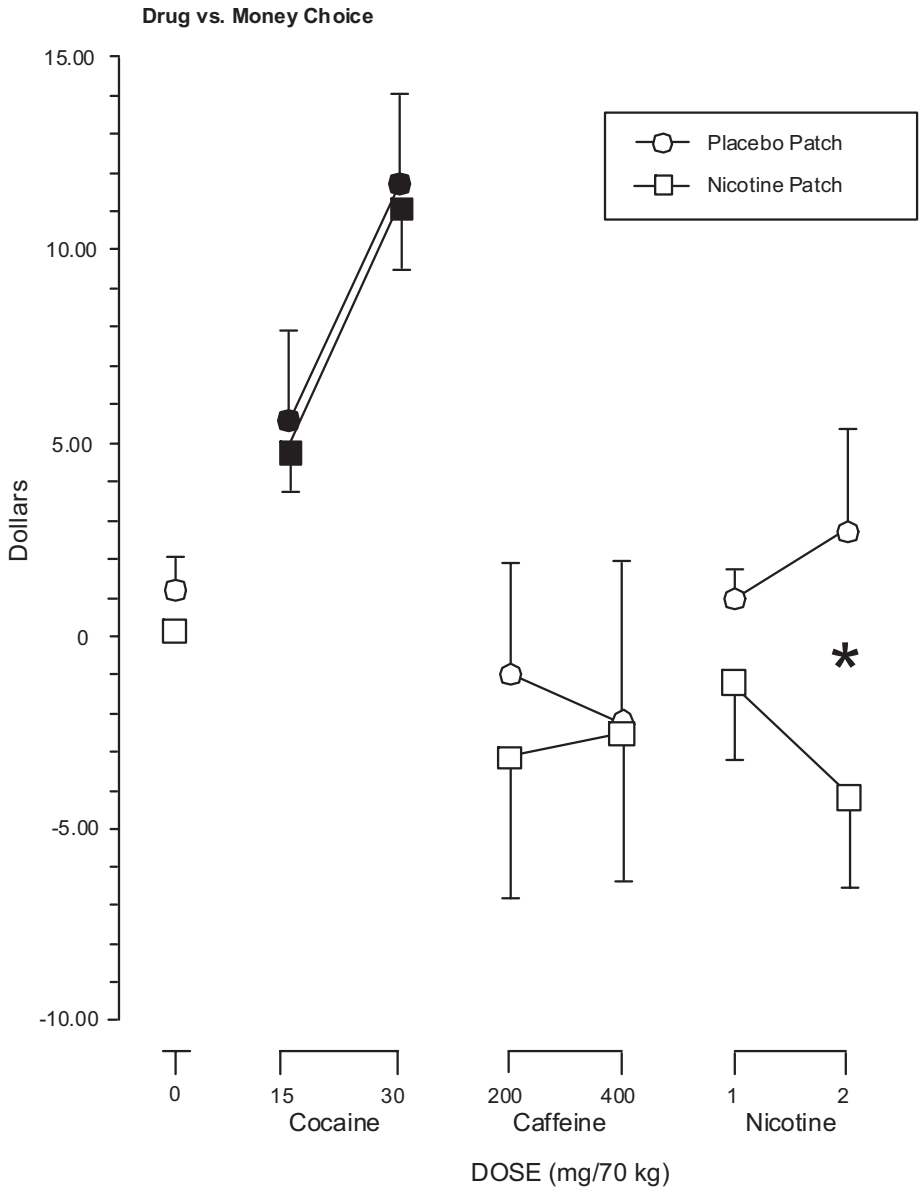


Figure 3. Effects of intravenous placebo, cocaine, caffeine, and nicotine on monetary values (crossover points) from the Drug Versus Money Multiple-Choice Form. Data points are means (n = 9). Error bars show 1 *SEM*; absence of error bar indicates *SEM* fell within the area of the symbol. Filled symbols indicate mean is significantly different from intravenous placebo ($p \leq .05$). The asterisk indicates a significant difference between the same drug dose in the nicotine maintenance and placebo maintenance phases ($p \leq .05$). From "Nicotine Maintenance Attenuates the Subjective and Reinforcing Effects of Intravenous Nicotine, But Not Cocaine or Caffeine, in Cigarette-Smoking Stimulant Abusers," by B.-F. X. Sobel, S. C. Sigmon, and R. R. Griffiths, 2004, *Neuropsychopharmacology, 29,* p. 998. Copyright 2004 by B.-F. X. Sobel, S. C. Sigmon, and R. R. Griffiths. Reprinted with permission.

Results from this initial open-label study suggest that depot buprenorphine was safe and well tolerated, with no significant side effects or adverse events. A single injection produced clinically relevant elevations in plasma buprenorphine levels that peaked at 2 days postdepot and gradually decreased over the study (see Figure 4). Both self-report and observer assessments suggested depot buprenorphine provided effective withdrawal suppression (see Figure 5), and changes in pupil diameter provided a physiological measure that generally reflected the subjective withdrawal ratings. No participant required supplemental medications for withdrawal relief after the depot administration. Depot bu-

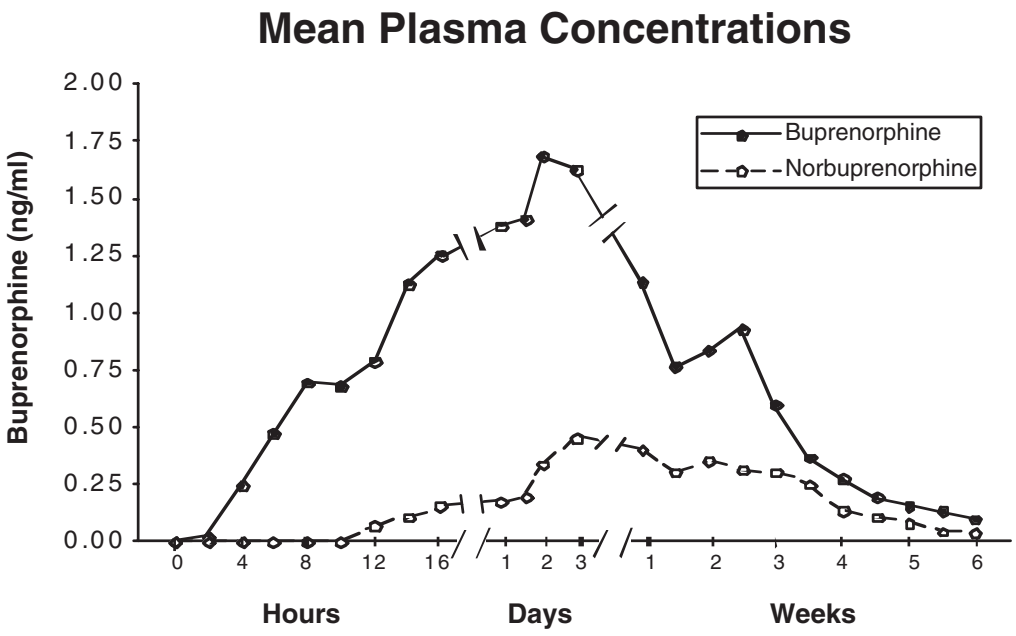
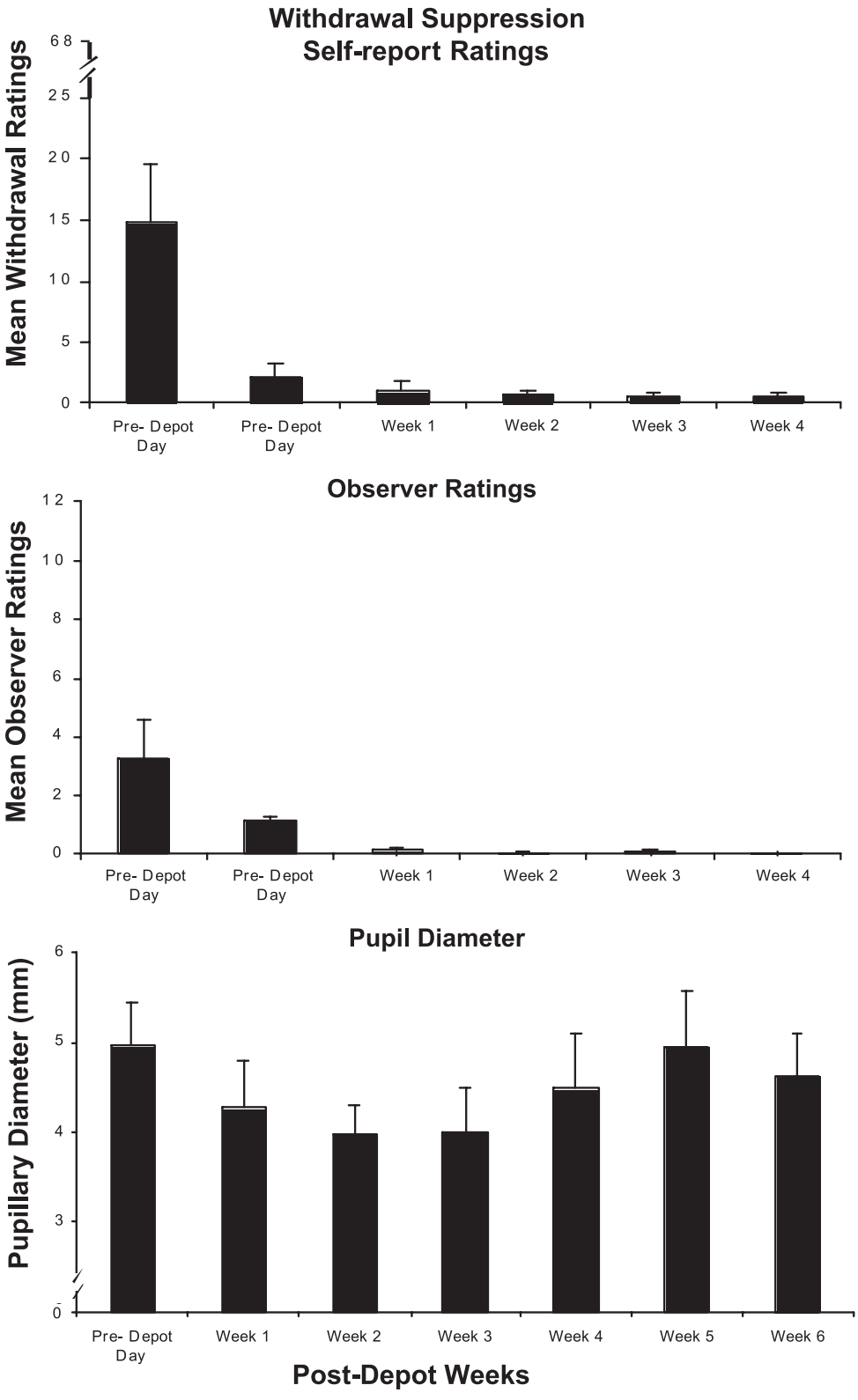


Figure 4. Plasma concentrations (ng/ml) of buprenorphine (filled symbols) and norbuprenorphine (open symbols) from blood samples collected repeatedly following depot administration ($n = 5$). From "Open-Label Trial of an Injection Depot Formulation of Buprenorphine in Opioid Detoxification," by B.-F. X. Sobel, S. C. Sigmon, S. L. Walsh, R. E. Johnson, I. A. Liebson, E. S. Nuwayser, et al., 2004, *Drug and Alcohol Dependence, 73,* p. 15. Copyright 2004 by Elsevier. Reprinted with permission.

prenorphine's efficacy in attenuating the effects of exogenous opioid challenge administrations also was notable. Ratings of opioid effects during Challenge Sessions 1 and 2 were at zero levels for all participants and then gradually increased but remained at remarkably low levels throughout the study (see Figure 6, top). Extent of opioid blockade was also seen in the peak change from baseline in pupil diameter following the opioid challenge (see Figure 6, bottom), with minimal pupil constriction following opioid challenge during Sessions 1 and 2. Mean peak change in pupil diameter gradually increased over Weeks 3–6, although these changes remained at very low values compared with that seen in previous studies with similar challenge doses. Although this study used a relatively modest dose of hydromorphone, overall the results suggest that depot buprenorphine substantially reduced responsiveness to opioid challenge, even as blood levels began to dissipate toward the end of the study period.

Results from this initial study suggest that this depot formulation may hold promise for enhancing delivery of buprenorphine treatment for opioid dependence. The important next step was to conduct a more rigorous investigation using double-blind, placebo-controlled methodology. In this second study, 15 opioid-dependent participants were randomized to receive a single depot injection of buprenorphine (58 mg) or placebo (Sigmon, Wong, Nuwayser, Chausmer, & Bigelow, 2004). Two participants, both of whom received placebo, terminated participation after depot administration. Thirteen participants (6 buprenorphine, 7 placebo) completed the 6-week study. As before, volunteers resided on the residential research unit, were assessed throughout the study for opioid withdrawal, and participated in weekly sessions to assess the ability of depot buprenorphine to attenuate physiological and subjective response to hydromorphone challenge. Depot buprenorphine provided more effective relief from withdrawal than placebo, as evidenced by significantly fewer buprenorphine participants requiring supplemental medications for withdrawal suppression after depot administration than those receiving placebo (see Figure 7). In the weekly challenge sessions, depot buprenorphine significantly reduced response on measures of subjective effects (see Figure 8) and pupillary diameter (see Figure 9).

Overall, results from both studies suggest that depot buprenorphine was effective in providing withdrawal suppression and opioid blockade. An injectable, sustained-release buprenorphine product could provide effective gradual clinical detoxification while simultaneously blocking the effects of exogenously administered opioids, thereby offering a more cost-effective alternative to traditional inpatient opioid detoxification. Depot buprenorphine also could reduce risk of illicit diversion and abuse by reducing or eliminating take-home medication during maintenance treatment, and it could improve patient compliance by preventing the need for patients to visit the treatment clinic daily or even weekly. Reducing the number of visits would simultaneously reduce the burdens of time and travel for


Withdrawal Suppression
Self-report Ratings
Mean Withdrawal Ratings
68
25
20
15
10
5
0
Pre- Depot Day
Pre- Depot Day
Week 1
Week 2
Week 3
Week 4
Observer Ratings
Mean Observer Ratings
12
10
8
6
4
2
0
Pre- Depot Day
Pre- Depot Day
Week 1
Week 2
Week 3
Week 4
Pupil Diameter
Pupillary Diameter (mm)
6
5
4
3
0
Pre- Depot Day
Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Post-Depot Weeks

patients, thereby making it easier for patients to participate in prosocial activities (e.g., employment, educational opportunities, family).

It is worth noting that because withdrawal symptoms did not emerge as blood levels of buprenorphine declined toward the end of the study, patients receiving depot buprenorphine in a clinical setting might not receive any pharmacological reminder of the need for their next dose. Therefore, it might be useful to use the psychosocial services mentioned above to prompt patients to visit the clinic for their next dose. It is also the case that there is no practical capability of removing the depot after it is administered. Concurrent medical conditions (e.g., need for analgesia, pregnancy) may present clinical management challenges, though it should be extremely rare that discontinuation of opioid dependence treatment would be the clinically appropriate response in such cases. Overall, it would be important to continue clinical and medical monitoring of patients who receive this treatment. Overall, sustained-release formulations of buprenorphine, such as the one investigated in these studies, may hold remarkable promise for enhancing the delivery of safe and effective opioid treatment.

Summary

Considering that polydrug use is typically the norm rather than the exception, identifying the extent to which pharmacological factors may influence drug reinforcement is critical to developing efficacious treatments for drug dependence. Although the above studies represent only a small number of such influences, they highlight the potential impact of issues such as the pharmacological interactions between commonly abused drugs and the extent to which chronic tolerance can impact the reinforcing effects of acutely administered drugs. In addition to its scientific importance, this area holds significant clinical relevance for vast numbers of people, including substance-abusing patients who use more than one drug, adolescents being prescribed stimulants for attention-deficit/hyperactivity disorder, and the average smoker seeking to quit smoking with the aid of nicotine replacement therapy. The development of novel formulations of currently available pharmacotherapies also represents an important and exciting area of psychopharmacology research. A sustained-release form of buprenorphine, for example, is just one example of using technology to enhance drug treatment while simultaneously minimizing clinical burden and risk. Overall, continued efforts to more fully characterize the host of potential pharmacological influences on the reinforcing effects of commonly abused drugs will be important to advancing a scientific understanding of drug dependence as well as to developing more effective strategies for reducing drug use.

Modulating Drug Reinforcement Using Nonpharmacological Factors

As discussed above, making other nondrug reinforcers available in the environment, contingent on an individual's abstinence from the target drug, can have orderly and robust effects on drug use. Contingency-management (CM) interventions represent one such empirically based approach that has been widely demonstrated to reduce drug self-administration. CM procedures provide incentives and disincentives contingent on changes in patients' behavior and typically involve the delivery of a tangible reward, often voucher-based incentives, contingent on the patient meeting a predetermined therapeutic target (Higgins et al., 1991; Higgins & Silverman, 1999). The most common targeted behavior is drug abstinence, wherein the patient earns voucher-based incentives for biochemically verified abstinence from recent drug use (e.g., negative urine sample or breath alcohol level). Vouchers not only provide an immediate reward to patients for drug abstinence but they are also then exchanged for goods and services in the community that further support a healthy, drug-free lifestyle (e.g., gym membership, educational classes, activities with spouse or family). Moreover, an escalating schedule of voucher earnings has been shown to specifically promote continuous durations of abstinence and to prevent relapse (Higgins et al., 1991; Roll & Higgins, 2000). Overall, extensive experimental research over the past 3 decades has demonstrated that CM is effective at promoting treatment retention and reducing drug use across a wide range of settings, types of drugs, and challenging clinical populations (Higgins & Silverman, 1999). My scientific efforts thus far primarily have focused on extending these treatments to reduce drug use among a variety of clinical populations. A brief review of some of these studies is provided below.

Extending CM to Reduce Illicit Drug Use Among Individuals With Serious Mental Illness

Substance abuse among individuals with schizophrenia and other severe mental illness is a serious public health

Figure 5 (opposite). Top: Mean self-report ratings of withdrawal during Weeks 1–4 of residential participation ($n = 5$). Middle: Mean observer ratings of withdrawal symptoms over the course of residential participation ($n = 5$). Bottom: Mean pupil diameter for the predepot day and for Postdepot Weeks 1–6. Pupil data are included for all 5 participants through Week 4 and for 4 participants for Weeks 5–6. The *y*-axis is presented on a smaller scale (3–6 mm) that represents a physiologically reasonable range for pupil diameters and allows more detailed inspection of the data. Error bars represent ± *SEM*. From "Open-Label Trial of an Injection Depot Formulation of Buprenorphine in Opioid Detoxification," by B.-F. X. Sobel, S. C. Sigmon, S. L. Walsh, R. E. Johnson, I. A. Liebson, E. S. Nuwayser, et al., 2004, *Drug and Alcohol Dependence, 73,* p. 17. Copyright 2004 by Elsevier. Reprinted with permission.

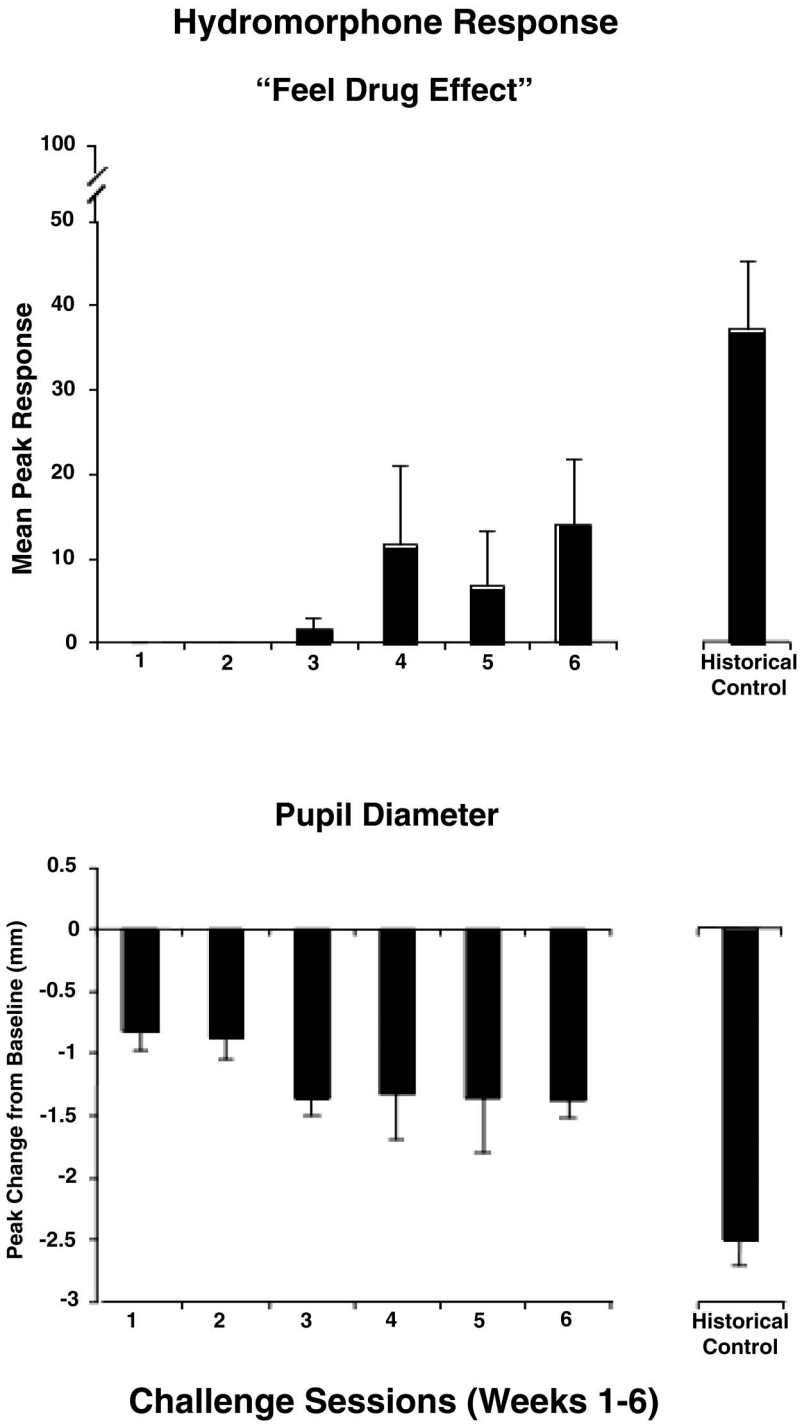


Figure 6. Top: Participants' mean peak ratings on the visual analog scale item "feel drug effect" for each of the six opioid challenge sessions. Mean ratings for a historical control sample of nondependent participants, for comparison purposes, are shown at far right. Bottom: Mean peak changes in pupil diameter (mm) in response to opioid challenge for each of the six weekly challenge sessions, with similar data from a historical control sample of nondependent participants shown at far right. Data for both measures include all 5 participants through Week 4 and 4 participants for Weeks 5–6. Error bars represent ± *SEM*. From "Open-Label Trial of an Injection Depot Formulation of Buprenorphine in Opioid Detoxification," by B.-F. X. Sobel, S. C. Sigmon, S. L. Walsh, R. E. Johnson, I. A. Liebson, E. S. Nuwayser, et al., 2004, *Drug and Alcohol Dependence, 73,* p. 18. Copyright 2004 by Elsevier. Reprinted with permission.

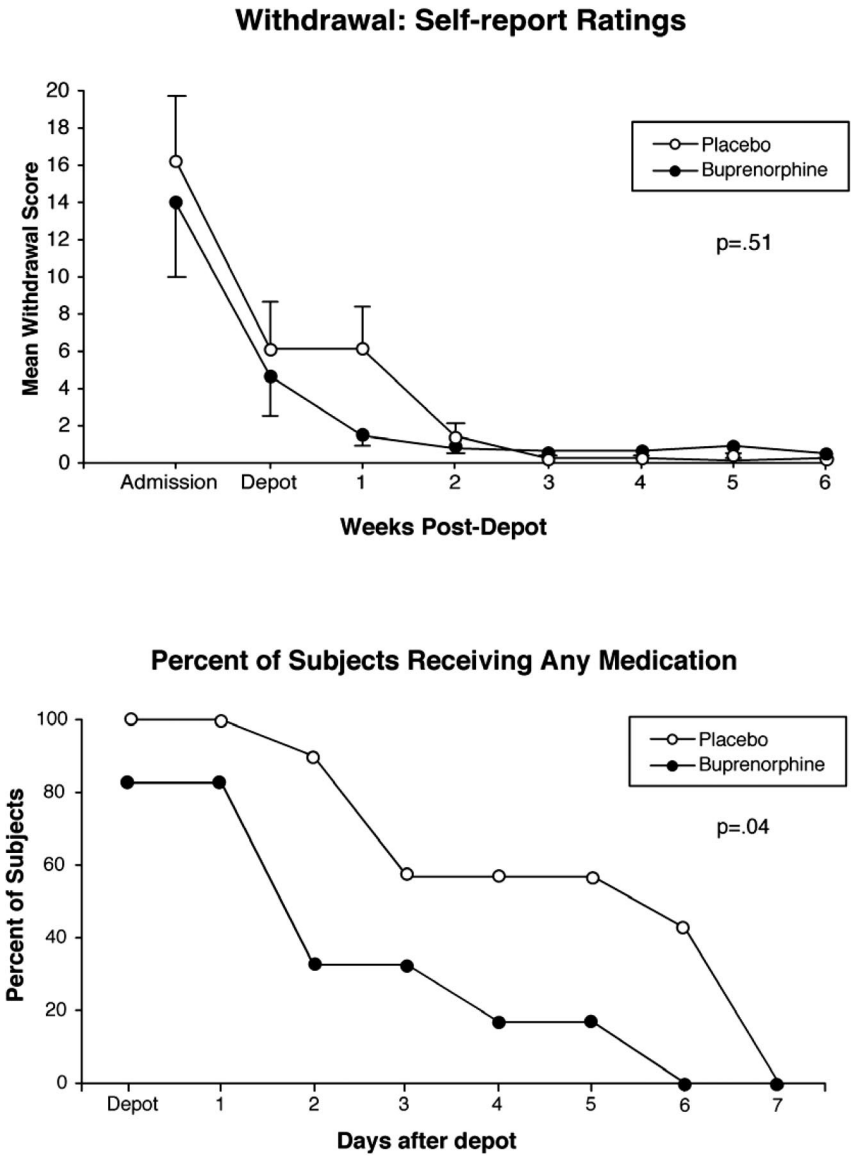


Figure 7. Top: Mean self-report ratings of withdrawal during Weeks 1–6 of the study ($n = 13$) for participants in the buprenorphine group (filled circles) and placebo group (open circles). Error bars represent ± *SEM*. Bottom: Percentages of participants in the buprenorphine and placebo groups receiving any rescue medication during the first week following depot administration ($n = 13$). From "Evaluation of Depot Buprenorphine: Placebo Comparison," by S. C. Sigmon, C. J. Wong, E. Nuwayser, A. Chausmer, and G. E. Bigelow, 2004, *Addiction, 99,* p. 1445. Copyright 2004 by Blackwell Publishing. Reprinted with permission.

problem and is associated with many adverse social, health, and psychiatric consequences (Bellack & Gearon, 1998; Carey, Carey, Weinhardt, & Gordon, 1997; Drake et al., 1991; Mueser et al., 1990; Regier et al., 1990). Marijuana use is the most common form of illicit drug use among individuals with schizophrenia as it is among the general population (Kandel, Chen, Warner, Kessler, & Grant, 1997; Negrete & Gill, 1999; Zisook et al., 1992). CM represents a form of substance abuse treatment that may have potential efficacy with this difficult-to-treat population. Several early studies provided early support for using CM interventions to reduce alcohol, nicotine, and cocaine use among individuals with schizophrenia (Peniston, 1988; Roll, Higgins, Steingard, & McGinley, 1998; Shaner et al., 1997). As the next step in this line of investigation, my colleagues and I conducted a feasibility study in the outpatient clinic setting at the University of Vermont to examine the sensitivity of marijuana use among individuals with serious mental illness to monetary incentives (Sigmon, Steingard, Badger, Anthony, & Higgins, 2000). Participants were 18 adults who

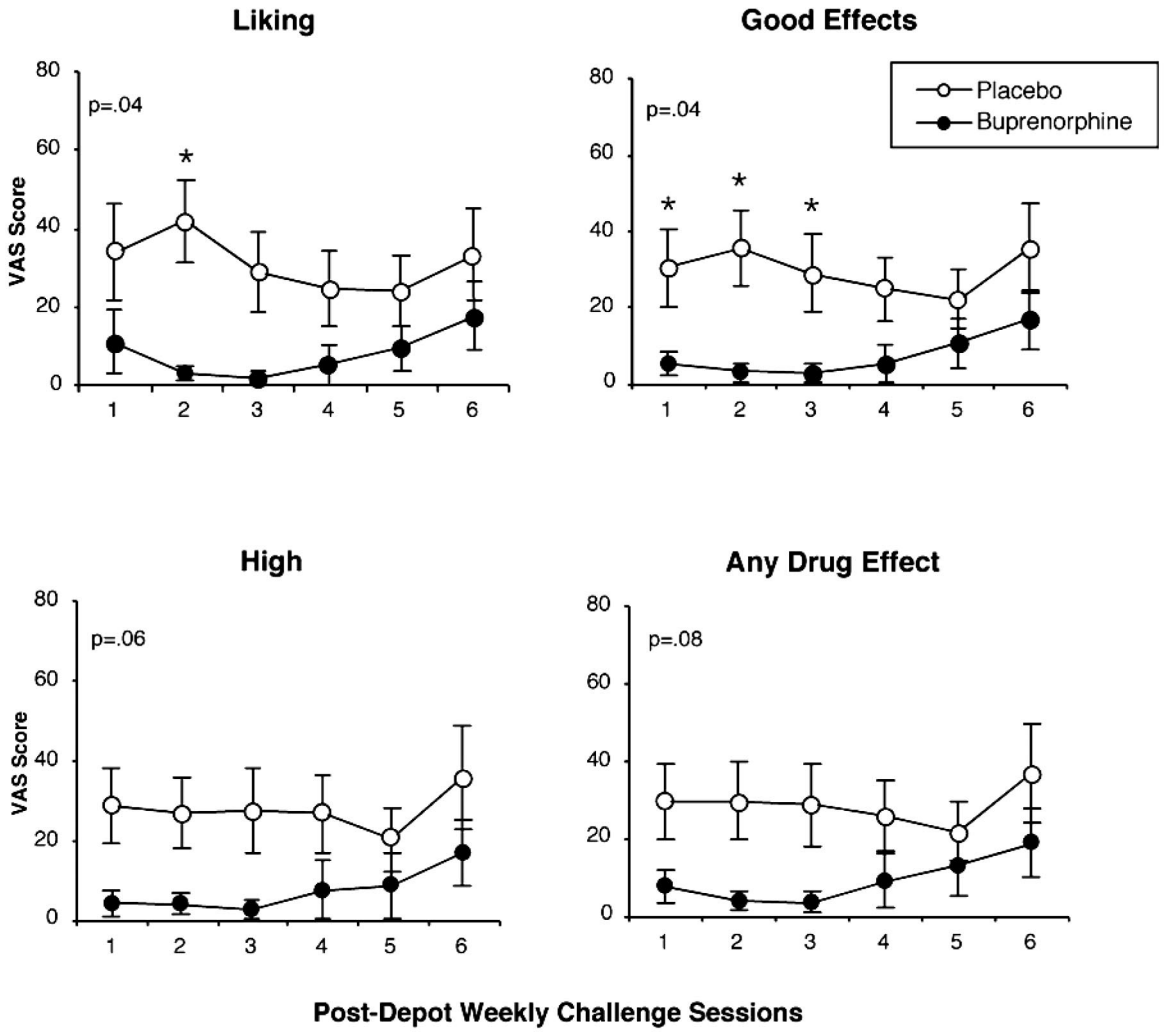


Figure 8. Participants' mean peak ratings on four visual analog scales for each of the six opioid challenge sessions. Asterisks indicate a significant difference between the buprenorphine and placebo groups at that weekly challenge session ($p \leq .05$). Error bars represent ± *SEM*. VAS = visual analog scale. From "Evaluation of Depot Buprenorphine: Placebo Comparison," by S. C. Sigmon, C. J. Wong, E. Nuwayser, A. Chausmer, and G. E. Bigelow, 2004, *Addiction, 99,* p. 1446. Copyright 2004 by Blackwell Publishing. Reprinted with permission.

were regular marijuana users and met *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; American Psychiatric Association, 1994) diagnosis for schizophrenia, schizoaffective disorder, bipolar disorder, or other psychotic disorders. The study was 25 weeks in duration and used a rigorous within-subjects experimental design that involved five 5-week conditions. Throughout the study, participants submitted urine specimens for urinalysis testing twice weekly under the observation of a same-gender staff member. During Parts 1 and 5 (baseline periods), participants were compensated $25 per specimen, independent of urinalysis results. During Parts 2–4, compensation was $25, $50, or $100 per specimen, contingent on marijuana-negative results.

The number of total (see Figure 10, top) and consecutive (see Figure 10, bottom) marijuana-negative specimens was significantly greater during the incentive conditions compared with either baseline. These results demonstrate that marijuana use among individuals with serious mental illness was sensitive to monetary incentives and lent empirical support to the potential feasibility of using CM to reduce substance abuse among patients with mental illness. My colleagues and I then conducted a subsequent study to examine whether this also held with voucher, rather than cash, incentives (Sigmon & Higgins, 2006). Because cash for some individuals can serve as a discriminative stimulus that may occasion drug seeking and use, vouchers are typically used as the incentive in CM interventions with clinical populations. Thus, in this second study, we sought to conduct the first investigation of the efficacy of voucher-based CM in reducing marijuana use among individuals with mental illness.

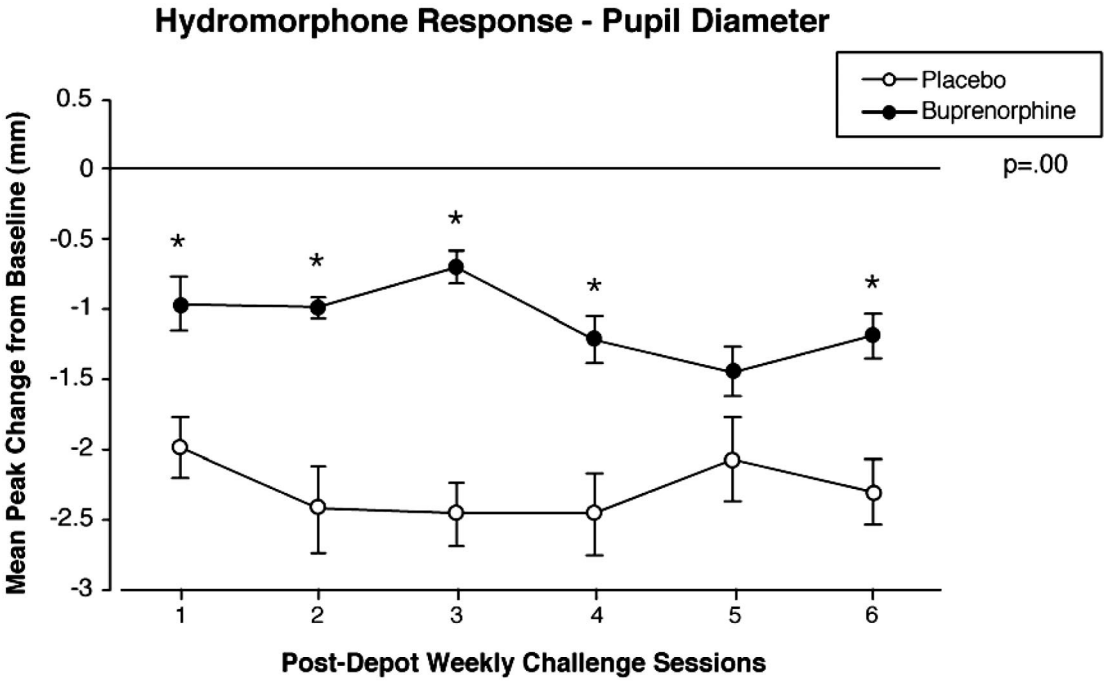
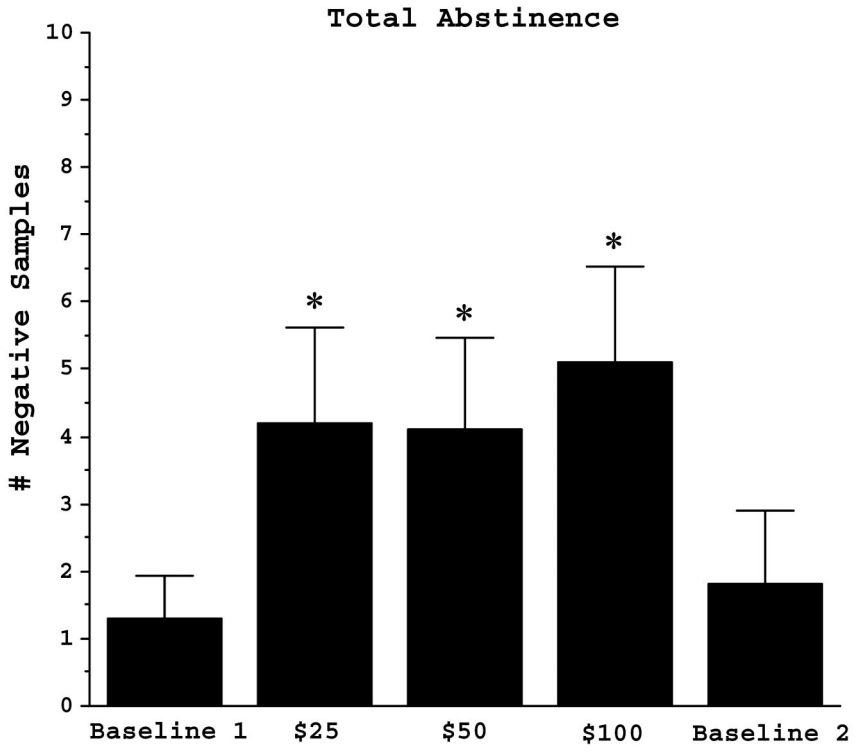


Figure 9. Mean peak changes in pupil diameter (from presession diameter) in response to opioid challenge for each of the six weekly challenge sessions. Asterisks indicate a significant difference between the buprenorphine and placebo groups at that weekly challenge session ($p \leq .05$). Error bars represent $\pm$ *SEM*. From "Evaluation of Depot Buprenorphine: Placebo Comparison," by S. C. Sigmon, C. J. Wong, E. Nuwayser, A. Chausmer, and G. E. Bigelow, 2004, *Addiction, 99,* p. 1446. Copyright 2004 by Blackwell Publishing. Reprinted with permission.

Similar to the previous study, this was a within-subject reversal design and consisted of three conditions: 4-week baseline, 12-week incentive, 4-week baseline. Throughout the study, participants submitted urine specimens twice weekly under the observation of a same-gender staff member. During each 4-week baseline, participants received a $10 voucher per specimen, independent of urinalysis results. During the 12-week incentive intervention, only marijuana-negative specimens earned vouchers. The voucher procedure used was similar to those used to reduce drug use among nonpsychiatric populations (Higgins, Alessi, & Dantona, 2002). The first negative specimen earned $5 in vouchers, and the value of each subsequent consecutive negative specimen increased by $2.50. To further increase the likelihood of continuous abstinence, participants earned a $10 bonus for each set of two consecutive negative specimens. Maximum voucher earnings possible for continuous abstinence was $930. Vouchers were exchangeable for goods and services in the community. Participants were 7 adults who were regular marijuana users and met *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.) diagnosis for schizophrenia, schizoaffective disorder, bipolar disorder, or other psychotic disorders. Both the percentage of total (see Figure 11, top) and consecutive (see Figure 11, bottom) marijuana-negative urine specimens were significantly greater during the incentive condition compared with either baseline. This study extends the sensitivity of marijuana use among individuals with schizophrenia to voucher-based CM. Taken together, the results from both studies suggest that CM may offer significant promise for reducing substance abuse among this difficult-to-treat population while simultaneously reducing the risk of misuse of incentives.

Extending CM to Reduce Cigarette Smoking Among Methadone-Maintained (MM) Patients

In a different but equally challenging population, my colleagues and I also used the outpatient clinic setting at the University of Vermont to evaluate the feasibility of using CM to reduce cigarette smoking among MM patients. Although MM treatment is a highly efficacious treatment for opioid dependence, ongoing abuse of other substances is common in this population (Ball & Ross, 1991; Stitzer & Sigmon, 2006). One of the more virulent forms of other substance abuse in this population is cigarette smoking, with the prevalence of current smoking in MM patients ranging from 80% to 100% (Chait & Griffiths, 1984; Clemmey, Brooner, Chutuape, Kidorf, & Stitzer, 1997; Richter, Gibson, Ahluwalia, & Schmelzle, 2001; Stark & Campbell, 1993). By contrast, estimates of current smoking in the general U.S. adult population are about 25% (Substance Abuse and Mental Health Services Administration, 2003).


Total Abstinence
Negative Samples
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1
2
3
4
5
6
7
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9
10
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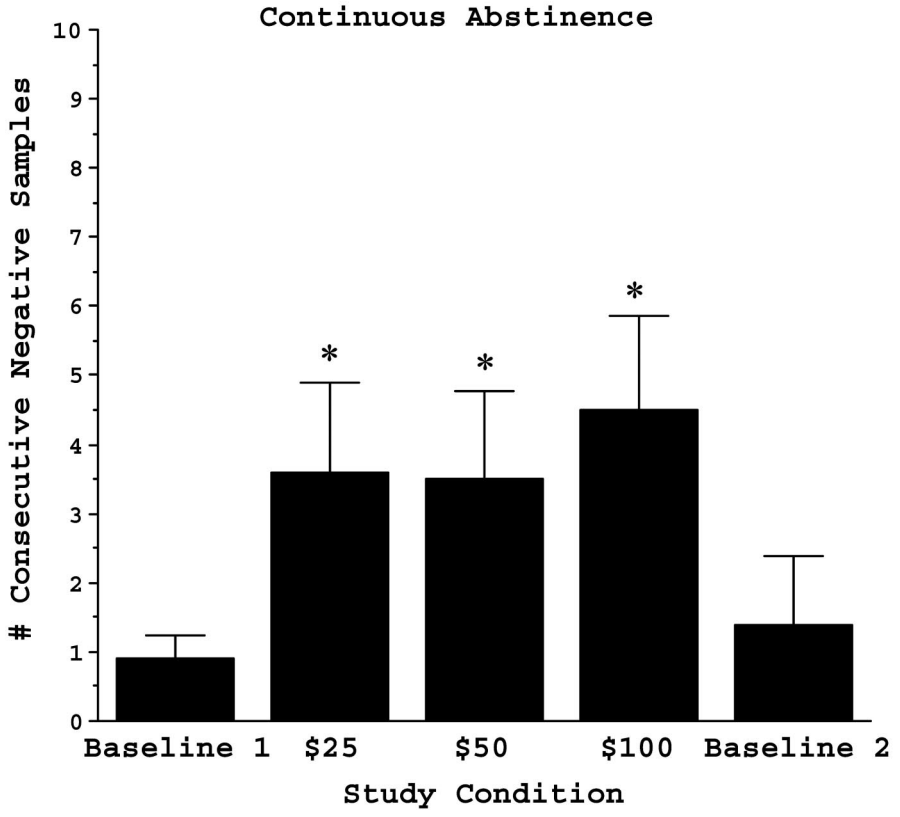
Baseline 1
$25
$50
$100
Baseline 2


Continuous Abstinence
Consecutive Negative Samples
0
1
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Study Condition

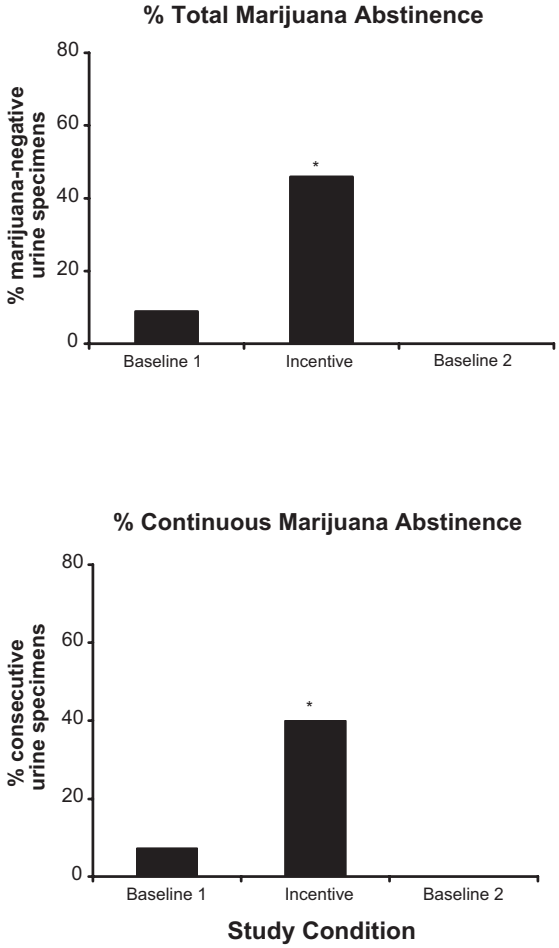

Figure 11. Percentage of total (top) and consecutive (bottom) marijuana-negative urinalysis results achieved across study conditions ($n = 7$). The labels on the *x*-axis represent the two 4-week baseline and the 12-week contingent payment conditions. The asterisk represents a significant difference between the percentage of marijuana-negative specimens in the incentive condition from baseline conditions ($p < .05$). From "Voucher-Based Contingent Reinforcement of Marijuana Abstinence Among Individuals With Serious Mental Illness," by S. C. Sigmon and S. T. Higgins, 2006, *Journal of Substance Abuse Treatment, 30,* p. 293. Copyright 2006 by Elsevier. Reprinted with permission.

As is the case in the general population, smoking among MM patients is associated with increased morbidity and mortality (Engstrom, Adamsson, Allebeck, & Rydberg, 1991; Hser, McCarthy, & Anglin, 1994).

Despite the striking rates of smoking among MM patients, little is known about how to help them quit smoking. Data from several early studies suggest the feasibility of using CM to reduce smoking among MM patients (Schmitz, Grabowski, & Rhoades, 1994; Shoptaw, Jarvik, Ling, & Rawson, 1996; Shoptaw et al., 2002), though one of the biggest challenges to date has been achieving sufficient continuous smoking abstinence during the early weeks of the cessation attempt to promote favorable longer term outcomes. Research on smoking suggests that a period of initial, sustained abstinence is critical for longer term success (Frosch, Nahom, & Shoptaw, 2002; Higgins et al., 2006; Kenford et al., 1994). Along these lines, my colleagues and I developed an intensive voucher-based CM program to promote early smoking abstinence during an initial 2-week cessation effort and are nearing completion of a small-scale pilot study evaluating this intervention. If it is effective in promoting early, continuous smoking abstinence during the initial days of the cessation attempt, we will then integrate procedures for maintaining this abstinence for the longer term.

Eligible participants must report smoking at least 10 cigarettes per day and be maintained on a stable methadone dose for the month before study intake, with no evidence of regular illicit-drug abuse. Participants are randomly assigned to a CM program with vouchers delivered contingent on biochemically verified abstinence (contingent voucher condition) or independent of smoking status and yoked to the schedule of voucher delivery in the contingent condition (noncontingent voucher condition). Both experimental conditions are 2 weeks in duration and include daily monitoring of smoking abstinence. Smoking is monitored using breath carbon monoxide levels for Days 1–5 of the study, and abstinence is defined as carbon monoxide less than or equal to 6 ppm. Beginning on Day 6 and continuing through the rest of the 14-day study, urine cotinine is used with smoking abstinence defined as cotinine less than or equal to 80 ng/ml. Contingent participants earn vouchers contingent on biochemical verification of recent smoking abstinence, with the initial negative test worth $9, each consecutive negative specimen increasing by $1.50, and a maximum possible earning of $262.50 for continuous abstinence. A positive test or failure to submit a scheduled specimen will earn no vouchers and reset the voucher values for the next negative specimen back to the initial $9 value. Noncontingent participants receive the same voucher amount described above but delivered independent of smoking status and yoked to the schedule of voucher earnings in the contingent voucher condition (Higgins, Wong, Badger, Haug Ogden, & Dantona, 2000; Silverman et al., 1996).

Figure 10 (opposite). Total (top) and consecutive numbers (bottom) of marijuana-negative urinalysis results achieved across study conditions. Labels on *x*-axis represent baseline conditions and the three different contingent payment conditions. Error bars represent ± 1 *SEM*. From "Contingent Reinforcement of Marijuana Abstinence Among Individuals With Serious Mental Illness: A Feasibility Study," by S. C. Sigmon, S. Steingard, G. J. Badger, S. L. Anthony, and S. T. Higgins, 2000, *Experimental and Clinical Psychopharmacology, 8*, p. 513. Copyright 2000 by the American Psychological Association. Reprinted with permission.

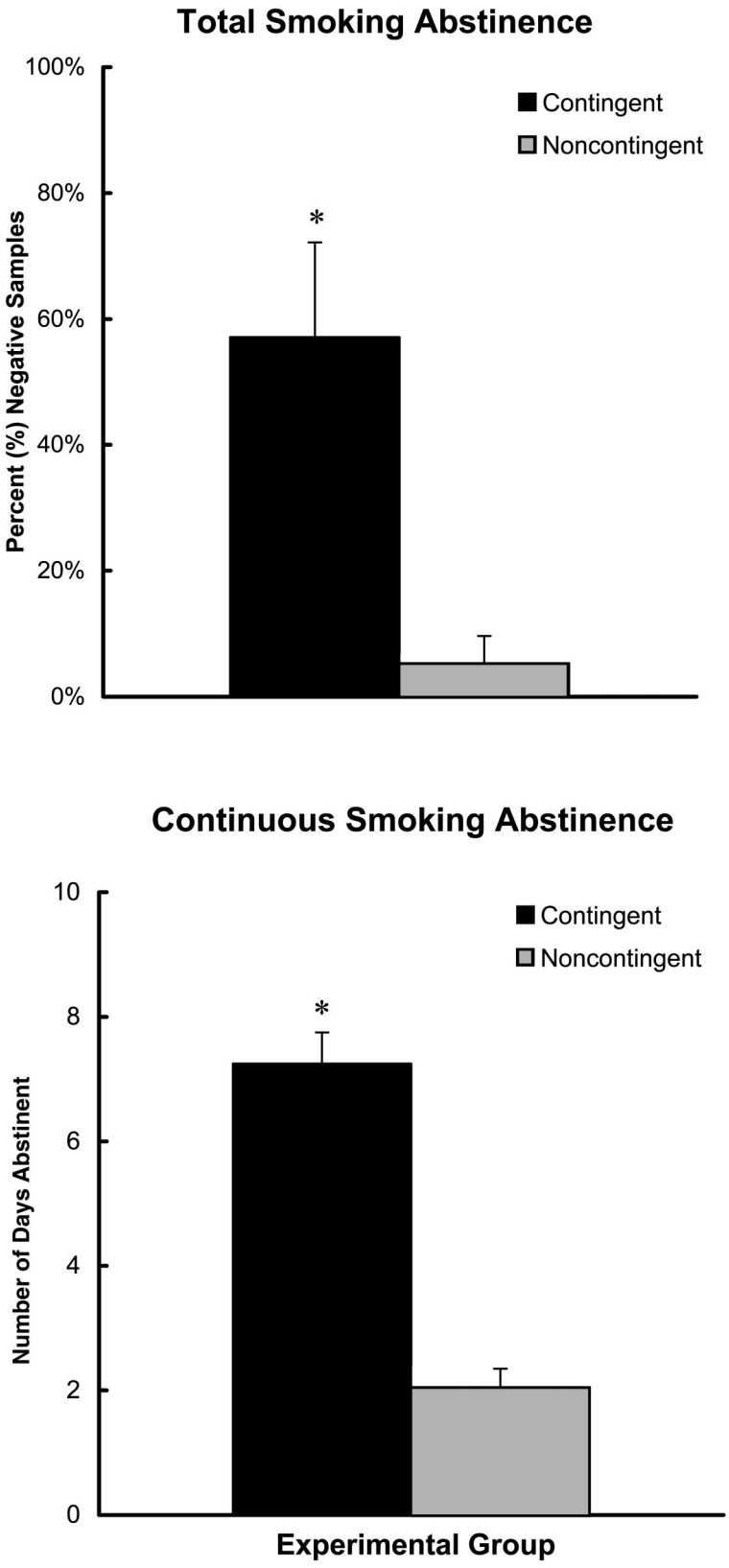

Figure 12. Percentage of total (top) and consecutive (bottom) smoking-negative urinalysis results achieved across the contingent (black bars) and noncontingent (gray bars) experimental groups. From "Incentive-Based Smoking Cessation for Methadone Patients: A Feasibility Study," by K. Dunn, S. C. Sigmon, and S. T. Higgins, 2006. Manuscript in progress.

Thus far, 16 MM smokers have enrolled in this ongoing pilot study. Contingent participants have achieved significantly more smoking abstinence, as evidenced by the greater percentage of smoking-negative samples among contingent (57%) compared with noncontingent participants (5%; see Figure 12, top). Longest duration of smoking abstinence is also significantly greater among contingent (7.3 days) than noncontingent (2.1 days; see Figure 12, bottom) participants. These preliminary results suggest that CM is an efficacious intervention for promoting initial smoking abstinence in a clinical sample of MM patients. The information obtained from this pilot will be used to develop a longer term intervention that seeks to maintain the initial abstinence achieved during this relatively brief 2-week intervention.

Summary

The above examples have demonstrated some recent efforts to extend the efficacy of using nondrug reinforcement, in the form of CM interventions, to reduce drug use across a variety of challenging populations. In still other recent studies, my colleagues and I have used the outpatient clinic setting to investigate more specific questions about the important parameters for using alternative reinforcers to compete with drug use. These have included relatively small-scale studies to examine what happens with repeated exposure to voucher-based CM (Sigmon, Correia, & Stitzer, 2004) and to compare the efficacy of various reinforcement schedules (Correia, Sigmon, Silverman, Bigelow, & Stitzer, 2005) as well as large-scale clinical trials to evaluate the contribution of individual components of a treatment for cocaine dependence that includes both CM and intensive behavioral counseling (Higgins et al., 2003). Although space is lacking to fully illustrate each of these studies here, it is fair to say that making alternative, nondrug reinforcers available contingent on drug abstinence can produce orderly and robust decreases in drug self-administration.

Conclusion

Drug use is driven by principles of reinforcement and is sensitive to influences in the environmental context in which it occurs. Both drug and nondrug influences can assert a powerful impact on a drug's reinforcing effects and, therefore, on the degree to which a particular drug comes to be used and abused. Understanding these influences will greatly enhance efforts to identify individuals at risk for developing problematic drug use as well as efforts to develop efficacious treatments for all forms of drug dependence.

References

Ahmadi, J. (2002). A controlled trial of buprenorphine treatment for opium dependence: The first experience from Iran. *Drug and Alcohol Dependence, 66,* 111–114.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

Ball, J. C., & Ross, A. (1991). *The effectiveness of methadone maintenance treatment.* New York: Springer-Verlag.

Bellack, A. S., & Gearon, J. S. (1998). Substance abuse treatment for people with schizophrenia. *Addictive Behaviors, 23,* 749–766.

Benowitz, N. L. (1998). Summary: Risks and benefits of nicotine. In N. L. Benowitz (Ed.), *Nicotine safety and toxicity* (pp. 185–194). New York: Oxford University Press.

Bickel, W. K., Stitzer, M. L., Bigelow, G. E., Liebson, I. A., Jasinski, D. R., & Johnson, R. E. (1988a). Buprenorphine: Dose-related blockade of opioid challenge effects in opioid dependent humans. *Journal of Pharmacology and Experimental Therapeutics, 247,* 47–53.

Bickel, W. K., Stitzer, M. L., Bigelow, G. E., Liebson, I. A., Jasinski, D. R., & Johnson, R. E. (1988b). A clinical trial of buprenorphine: Comparison with methadone in the detoxification of heroin addicts. *Clinical Pharmacology and Therapeutics, 43,* 72–78.

Biederman, J., Wilen, T., Mick, E., Spencer, T., & Faraone, S. V. (1999). Pharmacotherapy of attention-deficit/hyperactivity disorder reduces risk of substance use disorder. *Pediatrics, 104,* e20.

Bigelow, G. E., Sobel, B.-F. X., Terry, A. J., & Liebson, E. A. (2001, May). *Clinical evaluation of depot naltrexone*. Paper presented at the European Workshop: Alcohol and Drugs of Abuse, Brussels, Belgium.

Budney, A. J., Higgins, S. T., Hughes, J. R., & Bickel, W. K. (1993). Nicotine and caffeine use in cocaine-dependent individuals. *Journal of Substance Abuse, 5,* 117–130.

Bullingham, R. E. S., McQuay, H. J., Moore, A., & Bennett, M. R. D. (1980). Buprenorphine kinetics. *Clinical Pharmacology & Therapeutics, 28,* 667–672.

Carey, M. P., Carey, K. B., Weinhardt, L. S., & Gordon, C. M. (1997). Behavioral risk for HIV infection among adults with a severe and persistent mental illness: Patterns and psychological antecedents. *Community Mental Health Journal, 33,* 133–142.

Chait, L. D., & Griffiths, R. R. (1983). Effects of caffeine on cigarette smoking and subjective response. *Clinical Pharmacology & Therapeutics, 34,* 612–622.

Chait, L. D., & Griffiths, R. R. (1984). Effects of methadone on human cigarette smoking and subjective ratings. *Journal of Pharmacology and Experimental Therapeutics, 229,* 636–640.

Challman, T. D., & Lipsky, J. J. (2000). Methylphenidate: Its pharmacology and uses. *Mayo Clinic Proceedings, 75,* 711–721.

Clemmey, P., Brooner, R., Chutuape, M. A., Kidorf, M., & Stitzer, M. (1997). Smoking habits and attitudes in a methadone maintenance treatment population. *Drug and Alcohol Dependence, 44,* 123–132.

Correia, C. J., Sigmon, S. C., Silverman, K., Bigelow, G., & Stitzer, M. L. (2005). A comparison of voucher delivery schedules for the initiation of cocaine abstinence. *Experimental and Clinical Psychopharmacology, 13,* 253–258.

Cousins, M. S., Stamat, H. M., & de Wit, H. (2001). Acute doses of *d*-amphetamine and buproprion increase cigarette smoking. *Psychopharmacology, 157,* 243–253.

de Villiers, P. (1977). Choice in concurrent schedules and a quantitative formulation of the law of effect. In W. K. Honig & J. E. R. Staddon (Eds.), *Handbook of operant behavior* (pp. 233–287). Englewood Cliffs, NJ: Prentice-Hall.

Diamant, K., Fischer, G., Schneider, C., Lenzinger, E., Pezawas, L., Schindler, S., & Eder, H. (1998). Outpatient opiate detoxification treatment with buprenorphine: Preliminary investigation. *European Addiction Research, 4,* 198–202.

Di Chiara, G. (2000). Role of dopamine in the behavioural actions of nicotine related to addiction. *European Journal of Pharmacology, 393,* 295–314.

Drake, R. E., Wallach, M. A., Teague, G. B., Freeman, D. H., Paskus, T. S., & Clark, T. A. (1991). Housing instability and homelessness among rural schizophrenic patients. *American Journal of Psychiatry, 148,* 330–336.

Dunn, K., Sigmon, S. C., & Higgins, S. T. (2006). *Incentive-based smoking cessation for methadone patients: A feasibility study*. Manuscript in progress.

Eissenberg, T., Greenwald, M. K., Johnson, R. E., Liebson, I. A., Bigelow, G. E., & Stitzer, M. L. (1996). Buprenorphine's physical dependence potential: Antagonist-precipitated withdrawal in humans. *Journal of Pharmacology and Experimental Therapeutics, 276,* 449–459.

Engstrom, A., Adamsson, C., Allebeck, P., & Rydberg, U. (1991). Mortality in patients with substance abuse: A follow-up in Stockholm County, 1973–84. *International Journal of Addictions, 26,* 91–106.

Fredholm, B. B., Bättig, K., Holmén, J., Nehlig, A., & Zvartau, E. E. (1999). Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacological Reviews, 51,* 83–133.

Frosch, D. L., Nahom, D., & Shoptaw, S. (2002). Optimizing smoking cessation among the methadone maintained. *Journal of Substance Abuse Treatment, 23,* 425–430.

Fudala, P. J., Jaffe, J. H., Dax, E. M., & Johnson, R. E. (1990). Use of buprenorphine in the treatment of opiate addiction: II. Physiologic and behavioral effects of daily and alternate-day administration and abrupt withdrawal. *Clinical Pharmacology & Therapeutics, 47,* 525–534.

Garrett, B. E., & Griffiths, R. R. (1997). The role of dopamine in the behavioral effects of caffeine in animals and humans. *Pharmacology, Biochemistry and Behavior, 57,* 533–541.

Griffiths, R. R., Rush, C. R., & Puhala, K. A. (1996). Validation of the multiple-choice procedure for investigating drug reinforcement in humans. *Experimental and Clinical Psychopharmacology, 4,* 97–106.

Griffiths, R. R., Troisi, J. R., Silverman, K., & Mumford, G. K. (1993). Multiple-choice procedure: An efficient approach for investigating drug reinforcement in humans. *Behavioural Pharmacology, 4,* 3–13.

Hambrook, J. M., & Rance, M. J. (1976). The interaction of buprenorphine with the opiate receptor: Lipophilicity as a determining factor in drug-receptor kinetics. In H. W. Kosterlitz (Ed.), *Opiates and endogenous opioid peptides* (pp. 295–301). Amsterdam: Elsevier/North Holland, Biomedical Press.

Heishman, S. J., & Henningfield, J. E. (2000). Tolerance to repeated nicotine administration on performance, subjective, and physiological responses in nonsmokers. *Psychopharmacology, 152,* 321–333.

Henningfield, J. E. (1984). Behavioral pharmacology of cigarette smoking. In T. Thompson, P. B. Dews, & J. E. Barrett (Eds.), *Advances in behavioral pharmacology* (pp. 131–210). Orlando, FL: Academic Press.

Henningfield, J. E., Clayton, R., & Pollin, W. (1990). Involvement of tobacco in alcoholism and illicit drug use. *British Journal of Addiction, 85,* 279–292.

Henningfield, J. E., & Griffiths, R. R. (1981). Cigarette smoking and subjective response: Effects of *d*-amphetamine. *Clinical Pharmacology & Therapeutics, 30,* 497–505.

Higgins, S. T., Alessi, S. M., & Dantona, R. L. (2002). Voucher-based incentives: A substance abuse treatment innovation. *Addictive Behaviors, 27,* 887–910.

Higgins, S. T., Budney, A. J., Hughes, J. R., Bickel, W. K., Lynn, M., & Mortensen, A. (1994). Influence of cocaine use on cigarette smoking. *Journal of the American Medical Association, 272,* 1724.

Higgins, S. T., Delaney, D. D., Budney, A. J., Bickel, W. K., Hughes, J. R., Foerg, F., & Fenwick, J. W. (1991). A behavioral approach to achieving initial cocaine abstinence. *American Journal of Psychiatry, 148,* 1218–1224.

Higgins, S. T., Heil, S. H., Dumeer, A. M., Thomas, C. S., Solomon, L. J., & Bernstein, I. M. (2006). Smoking status in the initial weeks of quitting as a predictor of smoking-cessation outcomes in pregnant women. *Drug and Alcohol Dependence, 85,* 138–141.

Higgins, S. T., Heil, S. H., & Lussier, J. P. (2004). Clinical implications of reinforcement as a determinant of substance use disorders. *Annual Review of Psychology, 55,* 431–461.

Higgins, S. T., Sigmon, S. C., Wong, C. J., Heil, S. H., Badger, G. J., Donham, R., et al. (2003). Community reinforcement therapy for cocaine-dependent outpatients. *Archives of General Psychiatry, 60,* 1043–1052.

Higgins, S. T., & Silverman, K. (1999). *Motivating behavior change among illicit-drug abusers.* Washington, DC: American Psychological Association.

Higgins, S. T., Wong, C. J., Badger, G. J., Haug Ogden, D. E., & Dantona, R. L. (2000). Contingent reinforcement increases cocaine abstinence during outpatient treatment and 1 year of follow-up. *Journal of Consulting and Clinical Psychology, 68,* 64–72.

Himmelsbach, C. K. (1941). The morphine abstinence syndrome, its nature and treatment. *Annals of Internal Medicine, 15,* 829–839.

Hodos, W. (1961, September 29). Progressive ratio as a measure of reward strength. *Science, 134,* 943–944.

Hodos, W., & Kalman, G. (1963). Effects of increment size and reinforcer volume on progressive ratio performance. *Journal of the Experimental Analysis of Behavior, 6,* 387–392.

Hser, Y. I., McCarthy, W. J., & Anglin, M. D. (1994). Tobacco use as a distal predictor of mortality among long-term narcotic addicts. *Preventive Medicine, 23,* 61–69.

Istvan, J., & Matarazzo, J. D. (1984). Tobacco, alcohol, and caffeine use: A review of their interrelationships. *Psychological Bulletin, 95,* 301–326.

Jasinski, D. R., Pevnick, J. S., & Griffith, J. D. (1978). Human pharmacology and abuse potential of the analgesic buprenorphine. *Archives of General Psychiatry, 35,* 501–516.

Johnson, R. E., Jaffe, J. H., & Fudala, P. J. (1992). A controlled trial of buprenorphine treatment for opioid dependence. *Journal of the American Medical Association, 267,* 2750–2755.

Jones, H. E., & Griffiths, R. R. (2003). Oral caffeine maintenance potentiates the reinforcing and stimulant subjective effects of intravenous nicotine in cigarette smokers. *Psychopharmacology, 165,* 280–290.

Kandel, D. B., Chen, K., Warner, L., Kessler, R., & Grant, B. (1997). Prevalence and demographic correlates of symptoms of dependence on cigarettes, alcohol, marijuana and cocaine in the U.S. population. *Drug and Alcohol Dependence, 44,* 11–29.

Kelleher, R. T., & Morse, W. H. (1968). Determinants of the specificity of behavioral effects of drugs. *Reviews of Physiology, Biochemistry, and Experimental Pharmacology, 60,* 1–56.

Kenford, S. L., Fiore, M. C., Jorenby, D. E., Smith, S. S., Wetter, D., & Baker, T. B. (1994). Predicting smoking cessation: Who will quit with and without the nicotine patch. *Journal of the American Medical Association, 271,* 589–594.

Koob, G. F., & Nestler, E. J. (1997). The neurobiology of drug addiction. *Journal of Neuropsychiatry and Clinical Neurosciences, 9,* 482–497.

Kosten, T. R., & Kleber, H. D. (1988). Buprenorphine detoxification from opioid dependence: A pilot study. *Life Sciences, 42,* 635–641.

Lewis, J. W. (1985). Buprenorphine. *Drug and Alcohol Dependence, 14,* 363–372.

Ling, W., Charuvastra, C., Collins, J. F., Batki, S., Brown, L. S., Kintaudi, P., et al. (1998). Buprenorphine maintenance treatment of opiate dependence: A multicenter, randomized clinical trial. *Addiction, 93,* 475–486.

Lintzeris, N., Bell, J., Bammer, G., Jolley, D. J., & Rushworth, L. (2002). A randomized controlled trial of buprenorphine in the management of short-term ambulatory heroin withdrawal. *Addiction, 97,* 1395–1404.

Mazur, J. E. (1994). Choice. In J. E. Mazur (Ed.), *Learning and behavior* (3rd ed., pp. 334–365). Englewood Cliffs, NJ: Prentice-Hall.

Mello, N. K., Mendelson, J. H. (1980, February 8). Buprenorphine suppresses heroin use by heroin addicts. *Science, 207,* 657–659.

Mello, N. K., & Mendelson, J. H. (1986). Cigarette smoking: Interactions with alcohol, opiates and marijuana. In M. C. Braud & H. L. Ginzburg (Eds.), *Strategies for research on the interactions of drugs of abuse* (pp. 154–180) [Monograph]. Washington, DC: U.S. Government Printing Office.

Mello, N. K., Mendelson, J. H., & Kuehnle, J. C. (1982). Buprenorphine effects on heroin self-administration: An operant analysis. *Journal of Pharmacology and Experimental Therapeutics, 223,* 30–39.

Minor, R. L., Scott, B. D., Brown, D. D., & Winniford, M. D. (1991). Cocaine-induced myocardial infarction in patients with normal coronary arteries. *Annals of Internal Medicine, 115,* 797–806.

Moliterno, D. J., Willard, J. E., Lange, R. A., Negus, B. H., Boehrer, J. D., Glamann, D. B., et al. (1994). Coronary-artery vasoconstriction induced by cocaine, cigarette smoking, or both. *New England Journal of Medicine, 330,* 454–459.

Mueser, K. T., Yarnold, P. R., Levinson, D. F., Singh, H., Bellack, A. S., Kee, K., et al. (1990). Prevalence of substance abuse in schizophrenia: Demographic and clinical correlates. *Schizophrenia Bulletin, 16,* 31–54.

National Institute on Drug Abuse. (2001). *NIDA research report: Nicotine addiction* (NIH Publication No. 01–4342). Rockville, MD: Author.

Negrete, J. C., & Gill, K. (1999). Cannabis and schizophrenia: An overview of the evidence to date. In G. G. Nahas (Ed.), *Marihuana and medicine* (pp. 671–681). Totowa, NJ: Humana Press.

Nemeth-Coslett, R., Henningfield, J. E., Katz, J., & Goldberg, S. (1986). Effect of cocaine on rate of cigarette smoking. *Pharmacology, Biochemistry and Behavior, 25,* 303.

Peniston, E. G. (1988). Evaluation of long-term therapeutic efficacy of behavior modification program with chronic male psychiatric inpatients. *Journal of Behavior Therapy and Experimental Psychiatry, 19,* 95–101.

Perkins, K. A. (2002). Chronic tolerance to nicotine in humans and its relationship to tobacco dependence. *Nicotine and Tobacco Research, 4,* 405–422.

Perkins, K. A., Grobe, J. E., Epstein, L. H., Caggiula, A., Stiller, R. L., & Jacob, R. G. (1993). Chronic and acute tolerance to subjective effects of nicotine. *Pharmacology, Biochemistry and Behavior, 45,* 375–381.

Perkins, K. A., Grobe, J. E., Fonte, C., Goettler, J., Caggiula, A. R., Reynolds, W. A., et al. (1994). Chronic and acute tolerance to subjective, behavioral, and cardiovascular effects of nicotine in humans. *Journal of Pharmacology and Experimental Therapeutics, 270,* 628–638.

Preston, K. L., Bigelow, G. E., & Liebson, I. A. (1988). Buprenorphine and naloxone alone and in combination in opioid-dependent humans. *Psychopharmacology, 94,* 484–490.

Regier, D. A., Farmer, M. E., Rae, D. S., Locke, B. Z., Keith, S. J., Judd, L. L., & Goodwin, F. K. (1990). Comorbidity of mental disorders with alcohol and other drug abuse. *Journal of the American Medical Association, 264,* 2511–2518.

Richter, K. P., Gibson, C. A., Ahluwalia, J. S., & Schmelzle, K. H. (2001). Tobacco use and quit attempts among methadone maintenance clients. *American Journal of Public Health, 91,* 296–299.

Roll, J. M., & Higgins, S. T. (2000). A within-subject comparison of three different schedules of reinforcement of drug abstinence using cigarette smoking as an exemplar. *Drug and Alcohol Dependence, 58,* 103–109.

Roll, J. M., Higgins, S. T., Budney, A. J., Bickel, W. K., & Badger, G. J. (1996). A comparison of cocaine-dependent cigarette smokers on demographics, drug use and other characteristics. *Drug and Alcohol Dependence, 40,* 195–201.

Roll, J. M., Higgins, S. T., Steingard, S., & McGinley, M. (1998). Use of monetary reinforcement to reduce the cigarette smoking of persons with schizophrenia: A feasibility study. *Experimental and Clinical Psychopharmacology, 6,* 147–161.

Roll, J. M., Higgins, S. T., & Tidey, J. W. (1997). Cocaine use can increase cigarette smoking: Evidence from laboratory and naturalistic settings. *Experimental and Clinical Psychopharmacology, 5,* 263–268.

Rosen, M. I., Wallace, E. A., McMahon, T. J., Pearsall, R., Woods, S. W., Price, L. H., & Kosten, T. R. (1994). Buprenorphine: Duration of blockade of effects of intramuscular hydromorphone. *Drug and Alcohol Dependence, 35,* 141–149.

Rush, C. R., Higgins, S. T., Vansickel, A. R., Stoops, W. W., Lile, J. A., & Glaser, P. E. (2005). Methylphenidate increases cigarette smoking. *Psychopharmacology, 181,* 781–789.

Schmitz, J. M., Grabowski, J., & Rhoades, H. (1994). The effects of high and low doses of methadone on cigarette smoking. *Drug and Alcohol Dependence, 34,* 237–242.

Schottenfeld, R. S., Pakes, J. R., Oliveto, A., Ziedonis, D., & Kosten, T. R. (1997). Buprenorphine versus methadone maintenance for concurrent opiate dependence and cocaine abuse. *Archives of General Psychiatry, 54,* 713–720.

Schuh, K. J., & Griffiths, R. R. (1997). Caffeine reinforcement: The role of withdrawal. *Psychopharmacology, 130,* 320–326.

Schuster, C. R., Lucchesi, B. R., & Emley, G. S. (1979). The effects of *d*-amphetamine, meprobamate, and lobeline on the cigarette smoking behavior of normal human subjects. In N. Krasnegor (Ed.), *Cigarette smoking as a dependence process* (pp. 91–99) [Monograph]. Washington, DC: U.S. Government Printing Office.

Shaner, A., Roberts, L. J., Eckman, T. A., Tucker, D. E., Tsuang, J. W., Wilkins, J. N., & Mintz, J. (1997). Monetary reinforcement of abstinence from cocaine among mentally ill patients with cocaine dependence. *Psychiatric Services, 48,* 807–810.

Shoptaw, S., Jarvik, M. E., Ling, W., & Rawson, R. A. (1996). Contingency management for tobacco smoking in methadone-maintained opiate addicts. *Addictive Behaviors, 21,* 409–412.

Shoptaw, S., Rotheram-Fuller, E., Yang, X., Frosch, D., Nahom, D., Jarvik, M. E., et al. (2002). Smoking cessation in methadone maintenance. *Addiction, 97,* 1317–1328.

Sigmon, S. C., Correia, C., & Stitzer, M. L. (2004). Cocaine abstinence during methadone maintenance: Effects of repeated exposure to voucher-based reinforcement and predictive utility for response to abstinence incentive interventions. *Experimental and Clinical Psychopharmacology, 12,* 269–275.

Sigmon, S. C., & Higgins, S. T. (2006). Voucher-based contingent reinforcement of marijuana abstinence among individuals with serious mental illness. *Journal of Substance Abuse Treatment, 30,* 291–295.

Sigmon, S. C., Steingard, S., Badger, G. J., Anthony, S. L., & Higgins, S. T. (2000). Contingent reinforcement of marijuana abstinence among individuals with serious mental illness: A feasibility study. *Experimental and Clinical Psychopharmacology, 8,* 509–517.

Sigmon, S. C., Tidey, J. W., Badger, G. J., & Higgins, S. T. (2003). Acute effects of *d*-amphetamine on progressive-ratio performance maintained by cigarette smoking and money. *Psychopharmacology, 167,* 393–402.

Sigmon, S. C., Wong, C. J., Nuwayser, E., Chausmer, A., & Bigelow, G. E. (2004). Evaluation of depot buprenorphine: Placebo comparison. *Addiction, 99,* 1439–1449.

Silverman, K., Higgins, S. T., Brooner, R. K., Montoya, I. D., Cone, E. J., Schuster, C. R., & Preston, K. L. (1996). Sustained cocaine abstinence in methadone maintenance patients through voucher-based reinforcement therapy. *Archives of General Psychiatry, 53,* 409–415.

Smith, B. J., Jones, H. E., & Griffiths, R. R. (2001). Physiological, subjective and reinforcing effects of oral and intravenous cocaine in humans. *Psychopharmacology, 156,* 435–444.

Sobel, B.-F. X., Sigmon, S. C., & Griffiths, R. R. (2004). Nicotine maintenance attenuates the subjective and reinforcing effects of intravenous nicotine, but not cocaine or caffeine, in cigarette-smoking stimulant abusers. *Neuropsychopharmacology, 29,* 991–1003.

Sobel, B.-F. X., Sigmon, S. C., Walsh, S. L., Johnson, R. E., Liebson, I. A., Nuwayser, E. S., et al. (2004). Open-label trial of an injection depot formulation of buprenorphine in opioid detoxification. *Drug and Alcohol Dependence, 73,* 11–22.

Stark, M. J., & Campbell, B. K. (1993). Cigarette smoking and methadone dose levels. *American Journal of Drug and Alcohol Abuse, 19,* 209–217.

Stitzer, M. L., & Sigmon, S. C. (2006). Other substance use disorders: Prevalence, consequences, detection and management. In E. C. Strain & M. L. Stitzer (Eds.), *The treatment of opioid dependence* (pp. 365–397). Baltimore: Johns Hopkins University Press.

Strain, E. C., Stitzer, M. L., Liebson, I. A., & Bigelow, G. E. (1994). Comparison of buprenorphine and methadone in the treatment of opioid dependence. *American Journal of Psychiatry, 151,* 1025–1030.

Substance Abuse and Mental Health Services Administration. (2003). *Results from the 2002 National Survey on Drug Use and Health: National findings* (NHSDA Series H-22, DHHS Publication No. SMA 03–3836). Rockville, MD: Department of Health and Human Services, Office of Applied Studies.

Swanson, J. A., Lee, J. W., & Hopp, J. W. (1994). Caffeine and nicotine: A review of their joint use and possible interactive effects in tobacco withdrawal. *Addictive Behaviors, 19,* 229–256.

Tanda, G., & Goldberg, S. R. (2000). Alteration of the behavioral effects of nicotine by chronic caffeine exposure. *Pharmacology, Biochemistry and Behavior, 66,* 47–64.

Tidey, J. W., O'Neill, S. C., & Higgins, S. T. (2000). *d*-Amphetamine increases choice of cigarette smoking over monetary reinforcement. *Psychopharmacology, 153,* 85–92.

Walsh, S. L., Preston, K. L., Bigelow, G. E., & Stitzer, M. L. (1995). Acute administration of buprenorphine in humans: Partial agonist and blockade effects. *Journal of Pharmacology and Experimental Therapeutics, 274,* 361–372.

Walsh, S. L., Preston, K. L., Stitzer, M. L., Cone, E. J., & Bigelow, G. E. (1994). Clinical pharmacology of buprenorphine: Ceiling effects at high doses. *Clinical Pharmacology & Therapeutics, 55,* 569–580.

West, R. J., & Russell, M. A. H. (1987). Cardiovascular and subjective effects of smoking before and after 24 h of abstinence from cigarettes. *Psychopharmacology, 92,* 118–121.

Wiseman, E. J., & McMillan, D. E. (1996). Combined use of cocaine with alcohol or cigarettes. *American Journal of Drug and Alcohol Abuse, 22,* 577–587.

Zernig, G., O'Laughlin, I. A., & Fibiger, H. C. (1997). Nicotine and heroin augment cocaine-induced dopamine overflow in nucleus accumbens. *European Journal of Pharmacology, 337,* 1–10.

Zisook, S., Heaton, R., Moranville, J., Kuck, J., Jernigan, T., & Braff, D. (1992). Past substance abuse and clinical course of schizophrenia. *American Journal of Psychiatry, 149,* 552–553.

Zito, J. M., Safer, D. J., dosReis, S., Gardner, J. F., Boles, M., & Lynch, F. (2000). Trends in the prescribing of psychotropic medications to preschoolers. *Journal of the American Medical Association, 283,* 1025–1030.

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