Published in final edited form as:
Psychopharmacology (Berl). 2003 July ; 168(1-2): 31–41.

The reinstatement model and relapse prevention: a clinical perspective

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Abstract

Objectives—This commentary assesses the degree to which the reinstatement model is homologous to the human experience of relapse.

Results—A review of the literature suggests that the relationship is less clear than is often assumed, largely due to a lack of prospective data on the precipitants and process of relapse (especially relapse to heroin or cocaine abuse). However, reinstatement does not need to resemble relapse to have immediate clinical value; predictive validity as a medication screen would be sufficient. Whether the model has predictive validity is unknown, because, to date, very few clinical trials have tested medications that are effective in the reinstatement model, and even fewer have used designs comparable to those of reinstatement experiments. A clinical trial comparable to a reinstatement experiment would enroll participants who are already abstinent, and its main outcome measure would be propensity to undergo a specific type of relapse (e.g., relapse induced by stress or cues).

Conclusions—Until clinical and preclinical work are more comparable, criticisms of the reinstatement model's presumed shortcomings are premature.

The reinstatement model has generated a body of preclinical data that grows increasingly substantial and impressive (Shaham et al. 2003). Yet opinions remain divided about its relation to clinical realities (Marlatt 1996; Bergman and Katz 1998). In this commentary, we address the issues of whether reinstatement resembles relapse, whether it can be useful without resembling relapse, and why neither of those questions can yet be answered satisfactorily. We have drawn on clinical literature and on our own experiences working with substance abusers.

Does reinstatement resemble relapse? Maybe

In most published discussions of the reinstatement model, attention is drawn to the fact that the most widely studied precipitants of reinstatement in rats (drug priming, drug-associated cues, and stress) are provocatively similar to the precipitants of relapse in humans. This is typically taken as a point of commonality between the reinstatement model and the real-life experiences of recovered addicts. It is tempting to agree without further consideration; the assertion that priming, cues, and stress precipitate relapse is intuitively appealing and seems to accord with clinical experience. But how strong is the evidence that most relapses are precipitated by any of those three factors?

No definitive answer can be found in the clinical literature. Relapse is usually described retrospectively, with weeks or months intervening between the event and its recollection. This leaves ample time for the introduction of recall bias and the formation of post hoc explanations for the reporter's behavior. As an only slightly tangential illustration of the problem, consider

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the intuitively plausible prediction that abused children are at increased risk for later addiction. The prediction is confirmed when adult addicts are asked retrospectively about their childhoods —but not when abused and nonabused children are followed prospectively for incidence of addiction (Widom et al. 1999). This paradox may reflect a human tendency to ascribe one's behavior to something that seems, in hindsight, to make sense. In the case of relapse, the constructs that make sense to investigators (such as "stress-induced relapse") may be the same constructs that make sense to addicts as they try to piece together reasons for having relapsed.

The problems inherent in recall of relapses are surmountable by appropriate design and methodology. In studies of tobacco smokers, a technique called Ecological Momentary Assessment (EMA) has been used to enable outpatients to report their activities and moods before a lapse or relapse,[1] prospectively and in real time, using handheld data-collection devices (Shiffman et al. 1996). When EMA data are compared with retrospective reports gathered 12 weeks later from the same patients, large discrepancies emerge in reported triggers, activities, and moods during lapses (Shiffman et al. 1997). These discrepancies cannot be reliably correlated with patient characteristics, episode characteristics, or degree of confidence in recall accuracy (Shiffman et al. 1997). Reassuringly, EMA data in smokers tend to confirm that lapses and relapses are associated with smoking-associated cues and with negative mood (Shiffman et al. 1996), supporting assertions often made in support of the reinstatement model (if negative mood can be considered roughly homologous to stress). Similar, though less direct, findings were reported in an EMA study of alcoholics: negative mood predicted urge to drink, which, in turn, predicted drinking (Litt et al. 2000).

Will the same be true for heroin and cocaine? In the absence of real-time data, we are forced to rely on a small body of prospective studies whose time frames were not sensitive to episodes of acute stress. The general finding has been that prospective measures of stress predict lapse or relapse only when aggregated over time frames of 3 to 12 months, not (for example) week by week (Hall et al. 1991; McMahon 2001; Wasserman et al. 1998). Clearer evidence for acute-stress-induced (or cue-induced) relapse seems likely to emerge with real-time monitoring, but the issue has yet to be resolved empirically.

Does reinstatement need to resemble relapse? Maybe not, if it can screen treatment medications

The questions raised in Sect. 1 concern the model's face and construct validity, and although these questions are important, they may not be the first priority from a clinical point of view. More urgent is the question of predictive validity—whether the model can screen treatment medications. As scientists, of course, we are also interested in models with sufficient construct validity to help elucidate the pathophysiology of relapse. But as clinicians, we want treatments that work, and we do not immediately insist upon the relative luxury of knowing why they work.

Sarter and Bruno (2002) have argued that this approach is too myopic—that if a model has predictive validity without construct validity, it will find some of the right medications "for the wrong reasons" and miss other medications with novel mechanisms of action. The example cited was buspirone, an anxiolytic whose clinical efficacy was not predicted in traditional animal models of anxiety. In response, we would point out that anxiety disorders have long been pharmacologically treatable, while addiction relapse is not. Because no medication is available for relapse prevention, the field would be significantly advanced by a model that finds even one.

[1]In this commentary, *lapse* indicates any use of a drug by an individual who has been abstaining from that drug; *relapse* indicates a return to compulsive or harmful patterns of use. Operational definitions of these terms vary across studies

At what point, then, should a model of relapse be decreed inadequate? Reasonable guidance is available in an earlier review by Sarter et al. (1992) on animal models of amnesia as behavioral screens for cognitive enhancers. The review showed that the models were amassing an "overwhelming number" of false positives—medications that appeared promising when screened, but which failed clinical trials. An accumulation of false positives is a clear sign that a model needs refinement or abandonment, at least in its role as a screen for medications. From the point of view of treatment providers, this is the ground on which the reinstatement model will stand or fall.

But can it screen treatment medications? This remains to be tested

The reinstatement model has generated a large body of data on pharmacological interventions that prevent reinstatement; some of these data are summarized in Table 1. How do they compare with homologous data from clinical trials?

Currently, almost no such comparisons are possible. A clinical trial homologous to the reinstatement model would enroll former users who are currently abstinent (we leave aside, for now, the question of how abstinence is achieved) and would assess propensity to lapse or relapse. Clinical trials answering to the above description are startlingly rare, and the few that do exist have usually tested medications never tested in the reinstatement model. The lack of overlap can be seen by comparing Table 1 and Table 2. (Space limitations preclude a full discussion of the material in the tables, but the main purpose of the tables is illustrative.)

The closest points of overlap between preclinical and clinical work can be found in the alcohol literature. The findings appear, at first, to be mixed. Naltrexone, which blocks reinstatement (Lê et al. 1999; Ciccocioppo et al. 2002), has also been shown to prevent relapse in alcoholics (Streeton and Whelan 2001; Latt et al. 2002)—a finding that seems encouraging, except that the effect size is modest. Fluoxetine, which also blocks reinstatement (Lê et al. 1999), fails to prevent relapse in alcoholics (Kranzler et al. 1995). A reasonable explanation for the negative finding with fluoxetine, and for the modesty of the findings with naltrexone, is that each medication blocks only particular *subtypes* of reinstatement. As shown in Table 1, fluoxetine blocks reinstatement when the precipitant is footshock stress, but not when the precipitant is a priming dose of alcohol (Lê et al. 1999); naltrexone blocks reinstatement when the precipitant is a priming dose of alcohol (Lê et al. 1999) or an alcohol-associated cue (Ciccocioppo et al. 2002), but not when the precipitant is footshock stress (Lê et al. 1999). In the clinical trials cited here, the hypotheses were not precipitant-specific, and the trials were designed, powered, and analyzed accordingly (with no attempt, for example, to separate subtypes of relapse using EMA).[2]

In the literature on nicotine, cocaine, and heroin, we found no clinical trials assessing the relapse-prevention efficacy of medications that have been shown to block reinstatement.

If the search criteria are broadened to include clinical trials that did not literally examine relapse prevention, there emerges another modestly encouraging overlap between preclinical and clinical data: baclofen, which blocks priming-induced reinstatement of cocaine seeking in rats (Campbell et al. 1999), has also been shown to decrease cocaine craving and use in outpatients (though this was in an open-label pilot with only ten participants) (Ling et al. 1998). A more ambiguous case is that of buprenorphine, which appears to block priming-induced reinstatement of cocaine seeking in rats (Comer et al. 1993), but may not reduce cocaine use

[2]The alcohol literature also includes at least two relapse-prevention trials using acamprosate (Sass et al. 1996; Tempesta et al. 2000), which has been screened (with positive results) in the alcohol-deprivation model (Spanagel et al. 1996; Holter et al. 1997; Heyser et al. 1998). The alcohol-deprivation model differs from the reinstatement model in that there is no operant extinction procedure and alcohol is available again during the postdeprivation session (Lê and Shaham 2002)

in humans (Compton et al. 1995; Schottenfeld et al. 1997). This apparent false positive may be explicable in terms of buprenorphine-induced motor deficits in the rats (Y. Shaham, personal communication), or it may turn out not to have been false: data from our clinic support the possibility that buprenorphine slightly reduces cocaine use in methadone-maintained polydrug abusers (Montoya et al. 1996), and that this effect is statistically dissociable from its effect on heroin use (I.D. Montoya et al. submitted). The baclofen and buprenorphine findings do not strongly support the predictive validity of the reinstatement model, but neither do they constitute the "overwhelming number" of clear predictive failures for which Sarter et al. (1992) criticized other animal models.

In other clinical trials that did not literally assess relapse prevention, there is possible evidence that the reinstatement model has produced true *negatives*. For example, bromocriptine reinstates cocaine seeking in rats (Wise et al. 1990), and is *not* effective against cocaine abuse in clinical trials (Handelsman et al. 1997; Montoya et al. 2002). Similarly, the corticosteroid-synthesis inhibitor metyrapone reinstates heroin seeking in rats (Shaham et al. 1997), and the corticosteroid-synthesis inhibitor ketoconazole is *not* effective against cocaine or heroin abuse, perhaps even exacerbating them (Kosten et al. 2002). The detection of true negatives could support the specificity of the reinstatement model as a medication screen, but the homology between the preclinical and clinical data is incomplete: the clinical trials comprised patients who had not yet become abstinent, and thus they assessed the real-life homolog of self-administration rather than that of reinstatement. In rats, a drug that has no effect on the former may nonetheless block the latter (Shalev et al. 2002); the same may be true in humans. Therefore, even these negative findings are far from definitive.

If the search criteria are further broadened to include human laboratory studies, there are some additional points of overlap between the reinstatement literature and the human literature, but new complications arise. For example, reinstatement of cocaine seeking in rats is blocked by either ABT-431 (Self et al. 2000) or SCH 39166 (ecopipam) (Khroyan et al. 2000; Ciccocioppo et al. 2001),[3] and each of these has been tested in human laboratory studies. However, as shown in Table 3, cross-species comparison is impeded by differing administration schedules. For example, ABT-431 blocks reinstatement more effectively after chronic administration (Self et al. 2000), but the one published human laboratory study used acute administration only, leaving open the possibility that chronic administration would be more effective (Haney et al. 1999). Conversely, for ecopipam, human chronic-administration data are available (Haney 2001), but there are no chronic-administration reinstatement data with which they can be compared.

The tendency among preclinical investigators to screen medications with acute administration may be problematic, because in a clinical situation, those medications would be administered chronically. But there is a broader barrier to interpretation of the findings shown in Table 3, a barrier that would stand even if all the studies had used comparable schedules of administration. The human laboratory studies rely on surrogate endpoints that have sometimes turned out not to predict human behavior in daily life (Teoh et al. 1994;Weiss et al. 1995) or to predict it only weakly (Litt et al. 2000). Humans are aware that what happens in the laboratory is only a simulation of daily life, and that daily life will continue unchanged when the experiment ends. For a laboratory animal, the laboratory is the whole of life; the choices the animal makes within the context of a model are choices about its own survival. In that sense, a good animal model may be *less* far removed from day-to-day human life than a human psychopharmacological experiment is. None of this should be taken to deny the unique advantages of the latter (such as the experimenter's ability to give verbal instructions and collect verbal responses). But either

[3]ABT-431 and ecopipam are, respectively, an agonist and an antagonist at D_1 receptors. The seeming paradox of their common effectiveness is discussed by Alleweireldt et al. (2002)

approach requires a validity check against the gold standard of prospectively monitored day-to-day human behavior.

So what needs to be done in the short run?

As the preceding section shows, there is a remarkable paucity of overlap between the approaches used in reinstatement research and in clinical research on relapse prevention. Clinical and preclinical investigators can each help to narrow the gap.

Preclinical investigators could direct more of their efforts toward medication screening. Much of the research on the reinstatement model involves characterization of the mechanisms of reinstatement, such as the brain regions involved. This work is inherently interesting, but it is unlikely to help validate reinstatement as a model of relapse, because most of it cannot be done in humans. (Of course, it might be useful insofar as it suggests new medications to be tested in the model, and thereafter in the clinic.) Preclinical investigators should also keep an eye toward the ecological validity of their screening. For example, does the medication block reinstatement at a dosage whose interspecies-scaled equivalent is likely to be tolerated in humans? Does it continue to block reinstatement when administered chronically, as it would be administered in clinical practice?

Clinicians, meanwhile, should let the results of such screening guide their future clinical trials —in terms of participant selection, study design, choice of medication, and specificity of outcome measures. Participants should be abstinent former users; studies should center on real-time prospective evaluation of propensity to lapse and relapse. As for the choice of medication, Table 1 shows a large menu of potential medications suggested by preclinical studies. As mentioned earlier, most medications block only subtypes of reinstatement; thus, their specificity needs to be accounted for through a priori decisions about how relapse precipitants will be measured and classified, and studies need to be powered accordingly.

The multifactorial nature of relapse and the specificity of reinstatement-blocking medications suggest that treatment may require polypharmacy. Therefore, clinicians and preclinical investigators should focus on medications without known propensities for adverse interactions with other medications.

And what needs to be done in the long run?

From both ends—preclinical and clinical—the homology between drug-seeking behavior in rodents and in humans needs continued elucidation. One obstacle to that elucidation is the point of view wherein terms such as *descriptive* are used pejoratively. Science begins with good descriptions (Sidman 1960), and for relapse, there is much more describing to be done. The most obvious gap is the absence of real-time data on relapse in heroin and cocaine addicts. Collection of EMA data with handheld electronic devices has its drawbacks, but most of those drawbacks can be overcome (Litt et al. 1998); investigators who are reluctant to issue expensive EMA equipment to illicit-drug abusers should note that this has been done successfully with Ecstasy users (Lukas et al. 2002) and homeless crack cocaine users (Freedman et al. 2002).[4] Large-scale longitudinal EMA studies may help resolve issues of face and construct validity in the reinstatement model.

One such issue is that cessation of drug intake in the reinstatement model is the result of an extinction procedure rather than the result of choices made in a multioperant environment (which, for humans, would include entering treatment). This should matter only if the degree

[4]The EMA study by Freedman et al. (2002) focused on the feasibility of issuing and recovering equipment; no data on the process of relapse were reported

of choice involved in initial abstinence alters the precipitants or process of subsequent relapse. Perhaps insight could be gained through prospective assessment of relapse in addicts whose abstinence was initiated under different circumstances, such as self-initiated quitting, psychosocial treatment, depot-naltrexone injection, or involuntary inpatient (or in-prison) detoxification. (To our knowledge, relapse in former prisoners has been assessed only retrospectively, with emphasis on baseline predictors rather than on acute precipitants; Hiller 1996.) If the circumstances of abstinence initiation do make a difference, perhaps the reinstatement model could be refined so that it does not rely on extinction. For example, robust self-administration of drug might be reducible with the introduction of a high-magnitude nondrug reinforcer (as shown in rhesus monkeys by Nader and Woolverton 1991); preference for drug might then be reinstateable by a stressor. Potential relapse-prevention medications could then be screened for their ability to block the effect of the stressor.[5]

Another issue addressable by good descriptive data is whether humans show “incubation” of the propensity to relapse. In a procedure similar to that used in the reinstatement model, rats withdrawn from cocaine show a progressive increase in cue-induced responding for cocaine (in the absence of actual delivery of cocaine) over the course of 60 days. The clinical implications of this finding seem less dispiriting in light of the observation that responding returns to its initial low levels within 180 days (Y. Shaham, unpublished data). But the clinical occurrence of the phenomenon has yet to be demonstrated at all. One difficulty inherent in trying to demonstrate it is that each outpatient can have only one relapse per period of abstinence, leaving no way to know whether craving would have grown stronger beyond the point when the relapse occurred. It might be possible to study incubation in addicts released from settings in which they have undergone involuntary abstinence; if incubation occurs, latency to relapse should follow an inverted-U-shaped distribution as a function of the length of involuntary abstinence.

Finally, it might also be reassuring to extend the reinstatement/relapse homology to purely behavioral interventions. For example, relapse to heroin use in humans can be delayed or prevented with alternative reinforcers (Gruber et al. 2000). Can alternative reinforcers also block reinstatement? In one study, priming-induced reinstatement of cocaine seeking was not blocked by the presence of sucrose in the cage (Gosnell 2000). But in pilot work with a single rat, food-deprivation-stress-induced reinstatement (and responding during extinction) was blocked by access to toys (Y. Shaham, unpublished data). This line of research may not look especially alluring to most preclinical investigators, but its clinical relevance seems clear.

Conclusion

Most of the questions and issues raised in this commentary could be resolved by increased “crosstalk” between clinical and preclinical researchers. At an institutional level, there are instances of support for bench-to-bedside research. For example, in the US, the National Institute on Drug Abuse has established a funding mechanism called SPIRCAP (Strategic Program for Innovative Research on Cocaine Addiction Pharmacotherapy), and the National Institutes of Health have an intramural initiative called, fittingly, Bench to Bedside. However, recent Bench to Bedside awards do not appear to include any studies of addiction (Gallin et al. 2003). A brief search of the CRISP database of federally funded biomedical research projects (CRISP 2003) revealed no relapse studies of the kind we have suggested here, except for some studies of the natural history of cocaine dependence and predictors of relapse (which do not

[5]This suggested model is admittedly unsatisfying in several respects. The most obvious is that most animals would continue to self-administer some amount of drug throughout the experiment, thus sacrificing one of the major strengths of the reinstatement model: its ability to separate drug-seeking behavior from the pharmacological effects of the drug. The suggested model would also be unsuitable for assessment of priming-induced reinstatement. Still, this line of research could be useful for determining whether reinstatement in laboratory animals differs depending on the circumstances of cessation

appear to include EMA) and some clinical trials of bupropion or nicotine replacement for prevention of smoking relapse in postpartum women. Although there is justification for testing those agents for smoking relapse, that justification does not come from the reinstatement model, where neither agent has apparently been tested.

In pointing out the gap between bench and bedside, we intend no criticism of investigators on either side. Translational research faces a daunting barrier in information overload, and as journals and scientific organizations respond to the overload by becoming more specialized, the barrier only grows greater. It is understandable that preclinical investigators are not fully familiar with the patients and settings to which their work is meant to generalize; it is equally understandable that clinical investigators are not fully familiar with the ways in which preclinical work is conceptualized and carried out. But this shared lack of familiarity is now a rate-limiting step in validation of the reinstatement model. Until it is overcome, conclusions about the model's value to patients, or about its lack thereof, are premature.

Acknowledgements

We thank David Gorelick, M.D., for helpful comments on the manuscript.

References

Alleweireldt AT, Weber SM, Kirschner KF, Bullock B, Neisewander JL. Blockade or stimulation of D1 dopamine receptors attenuates cue reinstatement of cocaine-seeking behavior in rats. Psychopharmacology 2002;159:284–293. [PubMed: 11862361]

Baker DA, Tran-Nguyen TL, Fuchs RA, Neisewander JL. Influence of individual differences and chronic fluoxetine treatment on cocaine-seeking behavior in rats. Psychopharmacology 2001;155:18–26. [PubMed: 11374332]

Bergman J, Katz JL (1998) Behavioral pharmacology of cocaine and the determinants of abuse liability. In: Higgins ST, Katz JL (eds) Cocaine abuse: Behavior, pharmacology, and clinical applications. Academic Press, San Diego, pp 51–79

Bespalov AY, Zvartau EE, Balster RL, Beardsley PM. Effects of *N*-methyl-D-aspartate receptor antagonists on reinstatement of cocaine-seeking behavior by priming injections of cocaine or exposures to cocaine-associated cues in rats. Behav Pharmacol 2000;11:37–44. [PubMed: 10821207]

Brady KT, Myrick H, Henderson S, Coffey SF. The use of divalproex in alcohol relapse prevention: a pilot study. Drug Alcohol Depend 2002;67:323–330. [PubMed: 12127203]

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]

Ciccocioppo R, Sanna PP, Weiss F. Cocaine-predictive stimulus induces drug-seeking behavior and neural activation in limbic brain regions after multiple months of abstinence: reversal by D(1) antagonists. Proc Natl Acad Sci USA 2001;98:1976–1981. [PubMed: 11172061]

Ciccocioppo R, Martin-Fardon R, Weiss F. Effect of selective blockade of μ_1 δ opioid receptors on reinstatement of alcohol-seeking behavior by drug-associated stimuli in rats. Neuropsychopharmacology 2002;27:391–399. [PubMed: 12225696]

Comer SD, Lac ST, Curtis LK, Carroll ME. Effects of buprenorphine and naltrexone on reinstatement of cocaine-reinforced behavior. J Pharmacol Exp Ther 1993;267:1470–1477. [PubMed: 7903391]

Compton PA, Ling W, Charuvastra VC, Wesson DR. Buprenorphine as a pharmacotherapy for cocaine abuse: a review of the evidence. J Addict Dis 1995;14:97–114. [PubMed: 8555282]

CRISP Database Of Federally Funded Biomedical Research Projects (2003) http://crisp.cit.nih.gov Cited 13 Feb 2003

Crombag H, Grimm JW, Shaham Y. Effect of dopamine receptor antagonists on renewal of cocaine seeking by re-exposure to drug-associated contextual cues. Neuropsycho-pharmacology 2002;27:1006–1015.

De Vries TJ, Shaham Y, Homberg JR, Crombag H, Schuurman K, Dieben J, Vanderschuren LJ, Schoffelmeer AN. A cannabinoid mechanism in relapse to cocaine seeking. Nat Med 2001;7:1151–1154. [PubMed: 11590440]

Erb S, Shaham Y, Stewart J. The role of corticotropin-releasing factor and corticosterone in stress- and cocaine-induced relapse to cocaine seeking in rats. J Neurosci 1998;18:5529–5536. [PubMed: 9651233]

Erb S, Hitchcott PK, Rajabi H, Mueller D, Shaham Y, Stewart J. Alpha-2 adrenergic agonists block stress-induced reinstatement of cocaine seeking. Neuropsychopharmacology 2000;23:138–150. [PubMed: 10882840]

Ettenberg A, MacConell LA, Geist TD. Effects of haloperidol in a response-reinstatement model of heroin relapse. Psychopharmacology 1996;124:205–210. [PubMed: 8740040]

Freedman M, Pulley L, Abdolrussa B, McNamara C, Milby J, Schumacher J (2002) Ecological momentary assessment of crack cocaine relapse risk. In: 64th annual scientific meeting of the college on problems of drug dependence, San Juan, Puerto Rico. http://biopsych.com:81/cpdd02_web Cited 13 Feb 2003

Gallin JI, Gottesman MM (2003) Bench-to-bedside awards. National Institutes of Health, Bethesda, MD. http://www.cc.nih.gov/ccc/btb/awards.html Cited 10 March 2003

Gosnell BA (2000) The effects of sucrose availability on the reinstatement of cocaine-seeking. Soc Neurosci Abstr 485.16

Gottlieb LD, Horwitz RI, Kraus ML, Viscoli CM. Randomized controlled trial in alcohol relapse prevention: role of atenolol, alcohol craving, and treatment adherence. J Subst Abuse Treat 1994;11:253–258. [PubMed: 8072054]

Grimm JW, Hope BT, Wise RA, Shaham Y. Neuroadaptation: incubation of cocaine craving after withdrawal. Nature 2001;412:141–142. [PubMed: 11449260]

Grottick AJ, Fletcher PJ, Higgins GA. Studies to investigate the role of 5-HT2C receptors on cocaine and food maintained behaviour. J Pharmacol Exp Ther 2000;295:1183–1191. [PubMed: 11082456]

Gruber K, Chutuape MA, Stitzer ML. Reinforcement-based intensive outpatient treatment for inner city opiate abusers: a short-term evaluation. Drug Alcohol Depend 2000;57:211–223. [PubMed: 10661672]

Hall SM, Havassy BE, Wasserman DA. Effects of commitment to abstinence, positive moods, stress, and coping on relapse to cocaine use. J Cons Clin Psychol 1991;59:526–532.

Handelsman L, Rosenblum A, Palij M, Magura S, Foote J, Lovejoy M, Stimmel B. Bromocriptine for cocaine dependence: a controlled clinical trial. Am J Addict 1997;6:54–64. [PubMed: 9097872]

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]

Hays JT, Hurt RD, Rigotti NA, Niaura R, Gonzales D, Durcan MJ, Sachs DPL, Wolter TD, Buist AS, Johnston JA, White JD. Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation: a randomized, controlled trial. Ann Intern Med 2001;135:423–433. [PubMed: 11560455]

Heyser CJ, Schulteis G, Durbin P, Koob GF. Chronic acamprosate eliminates the alcohol deprivation effect while having limited effects on baseline responding for ethanol in rats. Neuropsychopharmacology 1998;18:125–133. [PubMed: 9430136]

Highfield D, Yap J, Grimm J, Shalev U, Shaham Y. Repeated lofexidine treatment attenuates stress-induced, but not drug cues-induced reinstatement of a heroin-cocaine mixture (speedball) seeking in rats. Neuropsychopharmacology 2001;25:320–331. [PubMed: 11522461]

Hiller ML (1996) Correlates of recidivism and relapse for parolees who received in-prison substance abuse treatment in Texas. In: Dissertation abstracts international: Section b: The sciences and engineering, vol 57(4-B):2866 Univ Microfilms International, USA

Holter SM, Landgraf R, Zieglgansberger W, Spanagel R. Time course of acamprosate action on operant ethanol self-administration after ethanol deprivation. Alcohol Clin Exp Res 1997;21:862–868. [PubMed: 9267536]

Khroyan TV, Barrett-Larimore RL, Rowlett JK, Spealman RD. Dopamine D1- and D2-like receptor mechanisms in relapse to cocaine-seeking behavior: effects of selective antagonists and agonists. J Pharmacol Exp Ther 2000;294:680–687. [PubMed: 10900248]

Kosten TS, Oliveto A, Sevarino KA, Gonsai K, Feingold A. Ketoconazole increases cocaine and opioid use in methadone maintained patients. Drug Alcohol Depend 2002;66:173–180. [PubMed: 11906804]

Kranzler HR, Burleson JA, Korner P, Del Boca FK, Bohn MJ, Brown J, Liebowitz N. Placebo-controlled trial of fluoxetine as an adjunct to relapse prevention in alcoholics. Am J Psychiatry 1995;152:391–397. [PubMed: 7864265]

Lando HA, Valanis BG, Lichtenstein E, Curry SJ, McBride CM, Pirie PL, Grothaus LC. Promoting smoking abstinence in pregnant and postpartum patients: a comparison of 2 approaches. Am J Manag Care 2001;7:685–693. [PubMed: 11464427]

Latt NC, Jurd S, Houseman J, Wutzke SE. Naltrexone in alcohol dependence: a randomised controlled trial of effectiveness in a standard clinical setting. Med J Australia 2002;176:530–534. [PubMed: 12064984]

Lê AD, Poulos CX, Harding S, Watchus J, Juzytsch W, Shaham Y. Effects of naltrexone and fluoxetine on alcohol self-administration and reinstatement of alcohol seeking induced by priming injections of alcohol and exposure to stress. Neuropsychopharmacology 1999;21:435–444. [PubMed: 10457541]

Lê AD, Shaham Y. Neurobiology of relapse to alcohol in rats. Pharmacol Therapeut 2002;94:137–156.

Lindblom N, De Villiers SH, Kalayanov G, Gordon S, Johansson AM, Svensson TH. Active immunization against nicotine prevents reinstatement of nicotine-seeking behavior in rats. Respiration 2002;69:254–260. [PubMed: 12097770]

Ling W, Shoptaw S, Majewska D. Baclofen as a cocaine anti-craving medication: a preliminary clinical study. Neuropsychopharmacology 1998;18:403–404. [PubMed: 9536455]

Litt MD, Cooney NL, Morse P. Ecological Momentary Assessment (EMA) with treated alcoholics: methodological problems and potential solutions. Health Psychol 1998;17:48–52. [PubMed: 9459069]

Litt MD, Cooney NL, Morse P. Reactivity to alcohol-related stimuli in the laboratory and in the field: predictors of craving in treated alcoholics. Addiction 2000;95:889–900. [PubMed: 10946438]

Liu X, Weiss F. Reversal of ethanol-seeking behavior by D1 and D2 antagonists in an animal model of relapse: differences in antagonist potency in previously ethanol-dependent versus nondependent rats. J Pharmacol Exp Ther 2002a;300:882–889. [PubMed: 11861794]

Liu X, Weiss F. Additive effect of stress and drug cues on reinstatement of ethanol seeking: exacerbation by history of dependence and role of concurrent activation of corticotropin-releasing factor and opioid mechanisms. J Neurosci 2002b;22:7856–7861. [PubMed: 12223538]

Longo LP. Olanzapine for cocaine craving and relapse prevention in 2 patients. J Clin Psychiatry 2002;63:595–596. [PubMed: 12143917]

Longo LP, Campbell T, Hubatch S. Divalproex sodium (Depakote) for alcohol withdrawal and relapse prevention. J Addictive Diseases 2002;21:55–64.

Lukas SE, Stull M, Cowan RL. Polydrug abuse patterns with MDMA (Ecstasy) among young adults. Drug Alcohol Depend 2002;66(suppl 1):S107.

Mantsch JR, Goeders NE. Ketoconazole does not block cocaine discrimination or the cocaine-induced reinstatement of cocaine-seeking behavior. Pharmacol Biochem Behav 1999a;64:65–73. [PubMed: 10494999]

Mantsch JR, Goeders NE. Ketoconazole blocks the stress-induced reinstatement of cocaine-seeking behavior in rats: relationship to the discriminative stimulus effects of cocaine. Psychopharmacology 1999b;142:399–407. [PubMed: 10229065]

Margolin A, Avants SK, Kosten TR. Mazindol for relapse prevention to cocaine abuse in methadone-maintained patients. Am J Drug Alcohol Abuse 1995;21:469–481. [PubMed: 8561098]

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

Martin-Fardon R, Ciccocioppo R, Massi M, Weiss F. Nociceptin prevents stress-induced ethanol, but not cocaine-seeking behavior in rats. Neuroreport 2000;11:1939–1943. [PubMed: 10884047]

McBride CM, Curry SJ, Lando HA, Pirie PL, Grothaus LC, Nelson JC. Prevention of relapse in women who quit smoking during pregnancy. Am J Public Health 1999;89:706–711. [PubMed: 10224982]

McCrady BS, Epstein EE, Hirsch LS. Maintaining change after conjoint behavioral alcohol treatment for men: outcomes at 6 months. Addiction 1999;94:1381–1396. [PubMed: 10615723]

McElroy SL, Weiss RD, Mendelson JH, Teoh SK, McAfee B, Mello NK (1989) NIDA Research Monograph 95:57–63

McKay JR, Alterman AI, Cacciola JS, Rutherford MJ, O'Brien CP, Koppenhaver J. Group counseling versus individualized relapse prevention aftercare following intensive outpatient treatment for cocaine dependence: initial results. J Cons Clin Psychol 1997;65:778–788.

McMahon RC. Personality, stress, and social support in cocaine relapse prediction. J Subst Abuse Treat 2001;21:77–87. [PubMed: 11551736]

Montoya ID, Gorelick DA, Preston KL, Umbricht A, Cheskin L, Contoreggi C, Johnson RE, Fudala PJ. Buprenorphine for treatment of dually-dependent (opiate and cocaine) individuals. NIDA Research Monograph 1996;162:178.

Montoya ID, Preston KL, Rothman R, Gorelick DA. Open-label pilot study of bupropion plus bromocriptine for treatment of cocaine dependence. Am J Drug Alc Abuse 2002;28:189–196.

Nader MA, Woolverton WL. Effects of increasing the magnitude of an alternative reinforcer on drug choice in a discrete-trials choice procedure. Psychopharmacology 1991;105:169–174. [PubMed: 1796123]

Niaura R, Abrams DR, Shadel WG, Rohsenow DJ, Monti PM, Sirota AD (1999) Addiction 94:685–695

Norman AB, Norman MK, Hall JF, Tsibulsky VL. Priming threshold: a novel quantitative measure of the reinstatement of cocaine self-administration. Brain Res 1999;831:165–174. [PubMed: 10411996]

Romach MK, Glue 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 Psychiat 1999;56:1101–1106. [PubMed: 10591286]

Sarter M, Hagan J, Dudchenko P. Behavioral screening for cognition enhancers: from indiscriminate to valid testing: part 1. Psychopharmacology 1992;107:144–159. [PubMed: 1615119]

Sarter M, Bruno JP (2002) Animal models in biological psychiatry. In: D'haenen H, den Boer JA, Willner P (eds) Biological psychiatry. Wiley, New York, pp 37–44

Sass H, Soyka M, Mann K, Zieglgansberger W. Relapse prevention by acamprosate: results from a placebo-controlled study on alcohol dependence. Arch Gen Psychiat 1996;53:673–680. [PubMed: 8694680]

Schenk S. Effects of the serotonin 5-HT(2) antagonist, ritanserin, and the serotonin 5-HT(1A) antagonist, WAY 100635, on cocaine-seeking in rats. Pharmacol Biochem Behav 2000;67:363–369. [PubMed: 11124402]

Schenk S, Partridge B, Shippenberg TS. U69593, a kappa-opioid agonist, decreases cocaine self-administration and decreases cocaine-produced drug-seeking. Psychopharmacology 1999;144:339–346. [PubMed: 10435406]

Schottenfeld RS, Pakes JR, Oliveto A, Ziedonis D, Kosten TR. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. Arch Gen Psychiat 1997;54:713–720. [PubMed: 9283506]

Schmidt LG, Kuhn S, Smolka M, Schmidt K, Rommelspacher H. Lisuride, a dopamine D2 receptor agonist, and anti-craving drug expectancy as modifiers of relapse in alcohol dependence. Prog Neuro-Psychopharmacol Biol Psych 2002;26:209–217.

Schmitz JM, Stotts AL, Rhoades HM, Grabowski J. Naltrexone and relapse prevention treatment for cocaine-dependent patients. Addict Behav 2001;26:167–180. [PubMed: 11316375]

See RE, Kruzich PJ, Grimm JW. Dopamine, but not glutamate, receptor blockade in the basolateral amygdala attenuates conditioned reward in a rat model of relapse to cocaine-seeking behavior. Psychopharmacology 2001;154:301–310. [PubMed: 11351937]

Self DW, Barnhart WJ, Lehman DA, Nestler EJ. Opposite modulation of cocaine-seeking behavior by D1- and D2-like dopamine receptor agonists. Science 1996;271:1586–1589. [PubMed: 8599115]

Self DW, Karanian DA, Spencer JJ. Effects of the novel D1 dopamine receptor agonist ABT-431 on cocaine self-administration and reinstatement. Ann NY Acad Sci 2000;909:133–144. [PubMed: 10911927]

Shaham Y, Stewart J. Effects of opioid and dopamine receptor antagonists on relapse induced by stress and re-exposure to heroin in rats. Psychopharmacology 1996;125:385–391. [PubMed: 8826544]

Shaham Y, Funk D, Erb S, Brown TJ, Walker CD, Stewart J. Corticotropin-releasing factor, but not corticosterone, is involved in stress-induced relapse to heroin-seeking in rats. J Neurosci 1997;17:2605–2614. [PubMed: 9065520]

Shaham Y, Erb S, Leung S, Buczek Y, Stewart J. CP-154,526, a selective, non peptide antagonist of the corticotropin-releasing factor type 1 receptor attenuates stress-induced relapse to drug seeking in cocaine-and heroin-trained rats. Psychopharmacology 1998;137:184–190. [PubMed: 9630005]

Shaham Y, Highfield D, Delfs JM, Leung S, Stewart J. Clonidine blocks stress-induced reinstatement of heroin seeking in rats: an effect independent of the locus coeruleus noradrenergic neurons. Eur J Neurosci 2000;12:292–302. [PubMed: 10651884]

Shaham Y, Shalev U, Lu L, de Wit H, Stewart J (2003) The reinstatement model of drug relapse: history, methodology and major findings. Psychopharmacology DOI 10.1007/s00213-002-1224-x

Shalev U, Yap J, Shaham Y. Leptin attenuates food deprivation-induced relapse to heroin seeking. J Neurosci 2001;21:RC129. [PubMed: 11160414]

Shalev U, Grimm JW, Shaham Y. Neurobiology of relapse to heroin and cocaine: a review. Pharmacol Rev 2002;54:1–42. [PubMed: 11870259]

Shiffman S, Paty JA, Gnys M, Kassel JD, Hickcox M. First lapses to smoking: within-subjects analysis of real-time reports. J Cons Clin Psychol 1996;64:366–379.

Shiffman S, Hufford M, Hickcox M, Paty JA, Gnys M, Kassel JD. Remember that? a comparison of real-time versus retrospective recall of smoking lapses. J Cons Clin Psychol 1997;65:292–300.

Sidman M (1960) Tactics of scientific research: evaluating experimental data in psychology. Basic Books, New York

Spanagel R, Holter SM, Allingham K, Landgraf R. Acamprosate and alcohol: 1. effects on alcohol intake following alcohol deprivation in the rat. . Eur J Pharmacol 1996;305:39–44. [PubMed: 8813529]

Spanagel R, Sillaber A, Zieglgansberger W, Corrigall WA, Stewart J, Shaham Y. Acamprosate suppresses the expression of morphine-induced sensitization in rats but does not affect heroin self-administration or relapse. Psychopharmacology 1998;139:391–401. [PubMed: 9809860]

Streeton C, Whelan G. Naltrexone, a relapse prevention maintenance treatment of alcohol dependence: a meta-analysis of randomized controlled trials. Alcohol Alcoholism 2001;36:544–552.

Tempesta E, Janiri L, Bignamini A, Chabac S, Potgieter A. Acamprosate and relapse prevention in the treatment of alcohol dependence: a placebo-controlled study. Alcohol Alcoholism 2000;35:202–209.

Teoh SK, Mello NK, Mendelson JH, Kuehnle J, Gastfriend DR, Rhoades E, Sholar W. Buprenorphine effects on morphine- and cocaine-induced subjective responses by drug-dependent men. J Clin Psychopharmacol 1994;14:15–27. [PubMed: 8151000]

Wasserman DA, Weinstein MG, Havassy BE, Hall SM. Factors associated with lapses to heroin use during methadone maintenance. Drug Alcohol Depend 1998;52:183–192. [PubMed: 9839144]

Weiss RD, Griffin ML, Hufford C. Craving in hospitalized cocaine abusers as a predictor of outcome. Am J Drug Alc Abuse 1995;21:289–301.

Widom CS, Weiler BL, Cottler LB. Childhood victimization and drug abuse: a comparison of prospective and retrospective findings. J Cons Clin Psychol 1999;67:867–880.

Wiesbeck GA, Weijers HG, Chick J, Naranjo CA, Boening J. Ritanserin in relapse prevention in abstinent alcoholics: results from a placebo-controlled double-blind international multicenter trial. Alcohol Clin Exp Res 1999;23:230–235. [PubMed: 10069551]

Wiesbeck GA, Weijers HG, Lesch OM, Glaser T, Toennes PJ, Boening J. Flupenthixol decanoate and relapse prevention in alcoholics: results from a placebo-controlled study. Alcohol Alcoholism 2001;36:329–334.

Wise RA, Murray A, Bozarth MA. Bromocriptine self-administration and bromocriptine-reinstatement of cocaine-trained and heroin-trained lever pressing in rats. Psychopharmacology 1990;100:355–360. [PubMed: 2315433]

Table 1

Preclinical studies of reinstatement in rats

	Alcohol	Nicotine	Cocaine	Heroin
Precipitants of reinstatement in rats				
Priming dose	Yes	Yes	Yes	Yes
Blocked by	Naltrexone (opioid antagonist) (Lê et al. 1999)	Nicotine antibodies (Lindblom et al. 2002)	ABT-431 (D_1 agonist) (Self et al. 2000)	Flupenthixol (DA antagonist) (Shaham and Stewart 1996)
	Naltrindole (δ-opioid antagonist) (Ciccocioppo et al., 2002)		Baclofen ($GABA_B$ agonist) (Campbell et al. 1999)	Haloperidol (D_2 antagonist) (Ettenberg et al. 1996)
			Buprenorphine (opioid partial agonist) (Comer et al., 1993)	Naltrexone (opioid antagonist) (Shaham and Stewart, 1996)
			Eticlopride (D_1 antagonist) (Khroyan et al. 2000)	Raclopride (D_2 antagonist) (Shaham and Stewart 1996)
			Flupenthixol (DA antagonist) (Khroyan et al. 2000)	SCH 23390 (D_1 antagonist) (Shaham and Stewart 1996)
			Nemonapride (D_1 antagonist) (Khroyan et al. 2000)	
			Ro 60-0175 ($5\text{-}HT_{2C}$ agonist) (Grottick et al. 2000)	
			SCH 23390 (D_1 antagonist)(Norman et al. 1999)	
			SCH 39166 (ecopipam) (D_1 antagonist) (Khroyan et al. 2000)	
			SKF 81297, 83959, 82958, or 38393 (D_1 agonists or partial agonists) (Self et al. 1996; Khroyan et al. 2000)	
			SR 141617A (cannabinoid antagonist) (DeVries et al. 2001)	
			U 69593 (κ agonist) (Schenk et al. 1999)	
			WAY 100653 ($5\text{-}HT_{1A}$ antagonist) (Schenk 2000)	
Not blocked by…	Fluoxetine (serotonin-uptake inhibitor) (Lê et al. 1999)	No data	Clonidine (α_2 agonist) (Erb et al. 2000)	Acamprosate (Spanagel et al. 1998)
	Naloxonazine (μ_1-opioid antagonist) (Ciccocioppo et al. 2002)		Fluoxetine (serotonin-uptake inhibitor) (Baker et al. 2001)	Leptin (given i.c.v.) (Shalev et al. 2001)
			Ketoconazole (corticosteroid- synthesis inhibitor) (Mantsch and Goeders 1999a)	
			Lofexidine (α_2 agonist) (Erb et al. 2000)	
			naltrexone (Comer et al. 1993)	
Cues	Yes	No data	Yes	Yes
Blocked by…	Eticlopride (D_2 antagonist) (Liu and Weiss 2002a)	No data	D-CPPene (NMDA antagonist) (Bespalov et al. 2000)	No data
	Naltrexone (opioid antagonist) (Ciccocioppo et al. 2002)		Raclopride (D_2 antagonist) (Crombag et al. 2002)	
	Naltrindole (δ-opioid antagonist) (Ciccocioppo et al. 2002)		SCH 23390 (D_1 antagonist) (See et al. 2001; Alleweireldt et al. 2002)	
	SCH 23390 (D_1 antagonist) (Liu and Weiss 2002a)		SCH 39166 (ecopipam) (D_1 antagonist) (Ciccocioppo et al. 2001)	
			SKF 81297 (D_1 agonist) (Alleweireldt et al. 2002)	
			SR141617A (cannabinoid antagonist) (De Vries et al. 2001)	
Not blocked by…	*d*-phe-CRF (CRF antagonist; given i.c.v.) (Liu and Weiss, 2002b)	No data	Memantine (NMDA antagonist) (Bespalov et al. 2000)	Lofexidine (α_2 agonist) (Highfield et al. 2001)
			SKF 38393 (D_1 partial agonist) (Alleweireldt et al. 2002)	
Food-deprivation stress	No data	No data	Yes	Yes
Blocked by…	No data	No data	No data	Leptin (given i.c.v.) (Shalev et al. 2001)
Footshock stress	Yes	Yes	Yes	Yes

	Alcohol	**Nicotine**	**Cocaine**	**Heroin**
Blocked by…	Fluoxetine (serotonin-uptake inhibitor) (Lê et al. 1999) *d*-phe-CRF (CRF antagonist; given i.c.v.) (Lê et al. 1999) CP-154,526 (CRF_1 antagonist) (Lê et al. 1999) Nociceptin (given i.c.v.) (Martin-Fardon et al. 2000)	No data	*d*-phe-CRF (CRF antagonist; given i.c.v.) (Erb et al. 1998) Clonidine (α_2 agonist) (Erb et al. 2000) CP-154,526 (CRF_1 antagonist) (Shaham et al. 1998) Ketoconazole (corticosteroid-synthesis inhibitor) (Mantsch and Goeders 1999b) Lofexidine (α_2 agonist) (Erb et al. 2000)	Clonidine (α_2 agonist) (Shaham et al. 2000) Lofexidine (α_2 agonist) (Shaham et al. 2000) α-helical-CRF (CRF_1 antagonist, given i.c.v.) (Shaham et al. 1997) CP-154,526 (CRF_1 antagonist) (Shaham et al. 1998) Flupenthixol (DA antagonist) (Shaham and Stewart 1996)
Not blocked by…	Naltrexone (opioid antagonist) (Lê et al. 1999)	No data	Nociceptin (given i.c.v.) (Martin-Fardon et al. 2000) SR 141617A (cannabinoid antagonist) (De Vries et al. 2001)	Acamprosate (Spanagel et al. 1998) Heroin (given chronically) (Shaham et al. 1996) Leptin (given i.c.v.) (Shalev et al. 2002) Metyrapone (corticosteroid- synthesis inhibitor) (Shaham et al. 1997) Naltrexone (opioid antagonist) (Shaham and Stewart 1996) Raclopride (D_2 antagonist) (Shaham and Stewart 1996) SCH 23390 (D_1 antagonist) (Shaham and Stewart 1996)

Table 2

Clinical studies of relapse

	Alcohol	Nicotine	Cocaine	Heroin
Human descriptive studies of relapse in real time	Yes; some support for stress-induced relapse (Litt et al. 2000)	Yes: some support for cue-induced relapse and stress-induced relapse (Shiffman et al. 1996)	No data	No data
Clinical trials literally examining relapse prevention (i.e., treatment administered to already abstinent patients, with relapse as the outcome measure)….				
Using interventions tested in the reinstatement model	Yes Fluoxetine: no effect, but outcome measures did not specifically include stress-induced relapse (Kranzler et al. 1995) Naltrexone: fewer relapses; fewer patients relapsed (Streeton and Whelan 2001, meta-analysis of 7 trials) Nalrexone: fewer relapses; fewer patients relapsed (Latt et al. 2002)	No data	No data	No data
Using interventions not tested in the reinstatement model	Yes: Acamprosate: relapses less severe (Tempesta et al. 2000) Acamprosate: fewer relapses (Sass et al. 1996) Atenolol: high dropout with or with-out medication (Gottlieb et al. 1994) Divalproex: fewer patients relapsed (Brady et al. 2002) Divalproex: fewer relapses (Longo et al. 2002) Flupenthixol: more relapses (Wiesbeck et al. 2001) Lisuride (D_2 agonist): relapses hastened (Schmidt et al. 2002) Ritanserin: no effect (Wiesbeck et al. 1999) Behavioral couples therapy or relapse-prevention therapy: relapse delayed by either (McCrady et al. 1999)	Yes: Bupropion: relapse delayed (Hays et al. 2001) Telephone counseling or point-of-service intervention for prevention of postpartum relapse: the former delayed but did not prevent relapse; the latter increased abstinence from 6 to 12 months Posttreatment, but not at 12 months (Lando et al. 2001) Relapse-prev therapy: delayed but did not prevent relapse (McBride et al. 1999) Cue-exposure treatment: no effect (Niaura et al. 1999)	Yes: Desipramine: effect not statistically significant (McElroy et al. 1989) Mazindol: effect not statistically significant (Margolin et al. 1995) Naltrexone: effect not statistically significant (Schmitz et al. 2001) Olanzapine: report of 2 cases, open-label (Longo 2002) Group counseling: in standard-counseling group, more patients remained Abstinent, but in relapse-prevention group, lapse was less likely to lead to relapse (McKay et al. 1997)	Yes: Contingency management: fewer patients relapsed; longer continuous abstinence (Gruber et al. 2000)

Table 3

Medication tested in the reinstatement model and in human laboratory studies of cocaine effects

		ABT-431(D_1 agonist)		Ecopipam (SCH 39166) (D_1 antagonist)	
		Acute	**Chronic**	**Acute**	**Chronic**
Rats	Reinstatement of cocaine seeking	Blockade of priming-induced reinstatement (Self et al. 2000)	Enhanced blockade of priming-induced reinstatement (Self et al. 2000)	Blockade of priming-induced reinstatement (Khroyan et al. 2000); blockade of cue-induced reinstatement (Ciccocioppo et al. 2002)	No data
Humans	Self-administration of cocaine in a laboratory setting	No effect (Haney 1999)	No data	No data	Increase with low dose of cocaine; no effect with high dose of cocaine (Haney 2001)
	Subjective effects of cocaine in a laboratory setting	Decrease (Haney 1999)	No data	Decrease (Romach 1999)	Increase (Haney 2001)
	Craving for cocaine in a laboratory setting	Decrease (trend) (Haney 1999)	No data	Decrease (Romach 1999)	Decrease (with placebo cocaine) (Haney 2001)