Published in final edited form as:

Pharmacol Ther. 2009 November ; 124(2): 235–247. doi:10.1016/j.pharmthera.2009.06.014.

Anti-relapse medications: Preclinical models for drug addiction treatment

Noushin Yahyavi-Firouz-Abadi and Ronald E. See*

Department of Neurosciences, Medical University of South Carolina, Charleston, SC

Abstract

Addiction is a chronic relapsing brain disease and treatment of relapse to drug-seeking is considered the most challenging part of treating addictive disorders. Relapse can be modeled in laboratory animals using reinstatement paradigms, whereby behavioral responding for a drug is extinguished and then reinstated by different trigger factors, such as environmental cues or stress. In this review, we first describe currently used animal models of relapse, different relapse triggering factors, and the validity of this model to assess relapse in humans. We further summarize the growing body of pharmacological interventions that have shown some promise in treating relapse to psychostimulant addiction. Moreover, we present an overview on the drugs tested in cocaine or methamphetamine addicts and examine the overlap of existing preclinical and clinical data. Finally, based on recent advances in our understanding of the neurobiology of relapse and published preclinical data, we highlight the most promising areas for future anti-relapse medication development.

Keywords

cocaine; drug screening; methamphetamine; reinstatement; relapse; self-administration

1. Introduction

Drug addiction is a chronic relapsing disorder, characterized by repetitive and compulsive drug-taking and drug-seeking behaviors, despite negative consequences (Jaffe, 1990; O'Brien & McLellan, 1996). In addiction or substance use disorders, relapse is defined as a return to drug-seeking/taking behavior after a period of self-imposed or forced abstinence. Addicts often have a persistent vulnerability to relapse to drug use after days or even years of abstinence, and prevention of relapse to drug-taking behavior is considered to be the most difficult aspect in the treatment of addiction (O'Brien, 1997). Treatment of addiction usually starts with medical and psychosocial assessments and relieving withdrawal symptoms (detoxification) that help the patient to achieve a drug-free state. However, the key to successful treatment is the long-term prevention of relapse by behavioral and pharmacological means (O'Brien, 2006). If drug-taking does not resume, homeostatic

© 2009 Elsevier Inc. All rights reserved.

*Corresponding author: Department of Neurosciences BSB416B, 173 Ashley Avenue Medical University of South Carolina Charleston, SC 29425, USA Tel.: 843-792-2487 Fax: 843-792-4423 Email: seere@musc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

mechanisms will gradually readapt to the absence of drug (LeBlanc et al., 1969) and many of the effects of prior drug use may ameliorate with time.

Despite clinical progress in treating the physical withdrawal syndromes produced by opiates, alcohol, and nicotine, successful treatments for all drug addictions are either completely lacking or clearly inadequate in terms of controlling the core addiction problems of drug craving and relapse (Nestler, 2002). Moreover, drugs of abuse produce pathological changes to the brain that can endure even after cessation of drug use (Hyman & Malenka, 2001; Kalivas & O'Brien, 2008). Consequently, recent preclinical research has focused on identifying long-term neuroadaptive changes and elucidating the behavioral, environmental, and neural mechanisms underlying drug relapse. By so doing, potential new avenues for relapse prevention may be developed. In patients, strategies to prevent relapse have traditionally involved counseling or psychotherapy, and more recently include pharmacotherapies that target clinical components of addictive illness (O'Brien, 2008). These medications have been used in order to diminish the strength of conditioned reflexes that lead to relapse and facilitate the development of new memories that produce natural rewards. Vaccines represent another experimental approach that is currently being evaluated in clinical trials (Martell et al., 2005; Sofuoglu & Kosten, 2006). In this review, we will discuss preclinical findings on medications that may reduce relapse to drug use, as well as relevant clinical data.

2. Animal models of relapse

2.1. Methodology

Most of the recent progress in understanding the underlying mechanisms of addiction and relapse has come from studies with animal models. Animals readily self-administer most drugs used by humans and show patterns of drug intake that mimic patterns seen in human users (Caine & Koob, 1993; Collins et al., 1984; Deroche-Gamonet et al., 2004). Although no animal model completely parallels human addiction, a number of laboratories have successfully developed and applied an animal model, termed the *reinstatement* model, to study factors that underlie relapse. In the learning literature, reinstatement refers to the resumption of a previously learned response (e.g., lever pressing behavior) that occurs when a subject is exposed noncontingently to the unconditioned stimulus (e.g., food or cocaine) after extinction (Bouton & Swartzentruber, 1991). Human and experimental animal studies have shown that drug craving and relapse following extended periods of abstinence are reliably triggered by exposure to: 1) a small, 'priming' dose of the drug, 2) cues previously associated with drug use, or 3) a stressful event. Accordingly, laboratory studies in humans have found that priming doses of cocaine, heroin, alcohol, or nicotine increased self-reports of craving in users of the respective drugs (de Wit, 1996; Jaffe et al., 1989). Moreover, stressful events and exposure to environmental cues associated with drug-taking behavior are known triggering factors to relapse in humans (Foltin & Haney, 2000; Shiffman, 1982; Sinha et al., 2006). Two major basic animal models of reinstatement have been developed to model relapse to addictive drug-seeking and drug-taking behavior: 1) conditioned place preference (CPP) based on Pavlovian conditioning, and 2) self-administration based on operant and Pavlovian conditioning.

2.1.1. Conditioned place preference—Several laboratories have developed reinstatement procedures using the CPP model in rats and mice. Reinstatement of a CPP is based upon Pavlovian drug conditioning, rather than instrumental conditioning, and purportedly models contextual cue-elicited drug-seeking behavior. In this procedure, subjects are initially trained to associate one compartment of a choice apparatus with drug injections and a second compartment with injections of the drug vehicle. Following training, subjects are given a choice between the two compartments on a drug-free test day, and

typically spend more time in the drug-paired environment (by definition, a CPP). Then, during an extinction phase, the acquired preference for the drug-paired context is extinguished by pairing injections of vehicle with both compartments (i.e., drug-associated and vehicle-associated), or by allowing subjects to explore the drug- and vehicle-associated compartments during daily sessions in the absence of the drug. Either procedure will produce extinction of the original drug-induced context-dependent place preference. Subsequently, tests for reinstatement of the CPP are carried out by exposing the animal to a relapse trigger, such as drug, stress, or other non-drug stimuli (Lu et al., 2000; Mueller & Stewart, 2000; Wang et al., 2000). The CPP model has also been used to study “reactivation” of acquired drug preference that is no longer observed following several drug-free weeks. The advantage of the CPP reinstatement model is that nonspecific motor effects of pharmacological manipulations may be less likely to influence behavior as the dependent measure is not operant-based responding. Moreover, it is methodologically easier, more affordable and can be achieved faster (sometimes by a single drug-context pairing) and is sensitive to relatively low drug doses (Aguilar et al., 2009; Tzschentke, 2007). However, there are several factors that limit the relevance of this model to compulsive and chronic drug use as seen in humans. First, it does not evaluate the primary reinforcing effects of drugs and drug-taking behavior, as there is no contingent use of the drug. Related to this problem is the inability to determine an animal's dynamic changes in drug intake over time. Second, noncontingent drug administration as used in CPP produces different pharmacokinetic and pharmacodynamic activity than seen during repeated contingent drug use. Moreover, total exposure to the drug is relatively low in CPP and dose-response effects have not been clearly demonstrated. Finally, some of the effects of CPP may reflect state-dependent learning due to discriminative stimuli properties of the test drug, rather than reinforcing efficacy.

2.1.2. Self-administration—The most commonly used animal model to study relapse to drug-seeking is the extinction-reinstatement model following intravenous drug self-administration. Self-administration models drug-taking behavior in humans and evaluates the primary rewarding properties of drugs. Reinstatement of drug-seeking after extinction implies the restoration of a concrete operant response. In this model, an animal is first surgically implanted with an intravenous catheter (although the drug can be administered through the oral route, as with ethanol) and allowed to acquire drug self-administration (e.g., lever-pressing or nose-poking) to a stable level. Subsequently, the drug-reinforced behavior is extinguished by withholding the drug reinforcer (substituting the drug solution with saline or by disconnecting the infusion pump). After a satisfactory degree of extinction is achieved (e.g., 20% or less responding during the last extinction session as compared with the first extinction session), the ability of acute exposure to a triggering stimulus (i.e., drug priming, stress, or drug-paired environmental cues) to reinstate operant responding as a measure of drug-seeking can be determined. Reinstatement is considered to have occurred if the animal responds at a rate above extinction and shows selectivity on the operandum that previously delivered the drug (e.g., presses on a previously “active” lever, as opposed to a previously non drug-paired “inactive” lever). Figure 1 illustrates a schematic graph of the reinstatement paradigm following drug self-administration and extinction.

Reinstatement of drug-seeking has been studied using different variations of the reinstatement model (Shalev et al., 2002): *between-session*, *within-session* and *between-within-session*. In the *between-session* paradigm, which is most commonly used, drug self-administration, extinction, and reinstatement tests are conducted during sequential daily sessions. In the *within-session* paradigm, self-administration training (1-2 h), extinction (3-4 h) and reinstatement tests are carried out on the same day. In the *between-within* paradigm, self-administration training occurs on different days. However, extinction and reinstatement tests are conducted on the same day after varying days of withdrawal (Shaham et al., 2003).

A modified relapse model of drug-seeking is one in which animals undergo forced abstinence in the home cage or an alternate environment without extinction trials following chronic self-administration (Fuchs et al., 2006). This abstinence model may have more direct relevance to addiction in humans, as addicts rarely experience explicit daily extinction of drug-seeking related to drug-paired cues and contexts during the withdrawal from drug use. Based on the above mentioned reasons for favoring the self-administration paradigm over CPP, in this review we will focus on studies using the reinstatement model in self-administration paradigm. For a recent review of the reinstatement model in CPP, see Aguilar et al., 2009.

2.2. Relapse triggering factors

2.2.1. Drug-induced relapse—Drug priming injection has been known for over three decades to be a potent stimulus to renew extinguished responding of drug-seeking (de Wit & Stewart, 1981; Gerber & Stretch, 1975). Priming injections robustly trigger relapse both after systemic administration and when given directly into the mesoaccumbens dopamine reward circuit, especially the ventral tegmental area (VTA) or the nucleus accumbens (NAc) (Stewart, 1984; Stewart & Vezina, 1988). A number of neurotransmitter systems regulate drug-induced relapse, including dopamine (DA), glutamate (Glu), endogenous opioids, γ -Aminobutyric acid (GABA), and endocannabinoids. However, growing evidence points to a convergence on a final common corticostriatal glutamatergic substrate (Kalivas & Volkow, 2005). Drug-primed reinstatement involves dorsomedial prefrontal cortex (dmPFC) glutamatergic projections to the NAc core and dopaminergic innervations of the dmPFC (McFarland & Kalivas, 2001). Current best evidence suggests that glutamatergic transmission plays a pivotal role in drug-primed relapse for different drugs of abuse, including cocaine and heroin (Knackstedt & Kalivas, 2009).

2.2.2. Stress-induced relapse—Negative affective states such as anger, anxiety, or depression, as well as stressful life events, can trigger relapse to drug-seeking and drug-taking in humans (Shiffman et al., 1996; Sinha et al., 1999). Thus, stress-induced reinstatement of drug-seeking behavior has been used to model this human situation (Erb et al., 1996; Koob & Le Moal, 2001; Shaham, Erb et al., 2000). Stress can be induced by a variety of precipitating factors, but in animal models, intermittent footshock (Erb et al., 1996; McFarland et al., 2004; Piazza & Le Moal, 1998) or pharmacologically-induced stress (Feltenstein & See, 2006; Lee et al., 2004; Shepard et al., 2004) have been the most successfully used stressors in the reinstatement paradigm (Epstein et al., 2006). Stress-induced reinstatement appears to involve the lateral tegmental noradrenergic nuclei (Shaham, Highfield et al., 2000) and their noradrenergic projections through the ventral noradrenergic bundle (Moore & Bloom, 1979) to the central nucleus of amygdala, bed nucleus of stria terminalis, hypothalamus, medial septum, and NAc (Shaham et al., 2003). As with drug-primed reinstatement, a final common glutamatergic corticostriatal pathway is engaged during stress-induced reinstatement (McFarland and Kalivas 2004).

2.2.3. Cue-induced relapse—A common risk factor to relapse in human addiction is exposure to environmental cues (sounds, sights, and other sensory stimuli) that were previously associated with drug use. As a consequence, conditioned cue-induced reinstatement of drug-seeking has been used to model this situation in animals (See, 2002). Different cues may precipitate reinstatement of drug-seeking behavior, including discrete cues, discriminative cues, and contextual cues. In studies on discrete cue-induced reinstatement, subjects are trained to self-administer a drug and each reward delivery is paired with discrete cues (e.g., lights or tones). Lever pressing is then extinguished in the absence of discrete cues and reinstated upon re-exposure to the cue. Drug-paired stimuli can be presented either as conditioned reinforcers and/or as discrete discriminative stimuli. In

the discriminative cue-induced procedure, rats are trained to self-administer a drug or saline in the presence of distinct discriminative stimuli in which one set of stimuli signals drug availability (S+) and the other set of stimuli signals saline availability (S-). Lever pressing is then extinguished in the absence of the discriminative stimuli and is resumed by exposure to the S+ (Weiss et al., 2000). For contextual reinstatement (alternatively called “renewal”), subjects are first trained to self-administer the drug with available cues (e.g., light, tone, odor) in one distinct context (drug-paired context) that act as occasion setters for the availability of the drug, and drug-reinforced behavior is extinguished in the presence of different sets of cues in another context (extinction context). These contexts are different in their tactile, visual, auditory, and/or olfactory features. Re-exposure of the subject to the drug-paired context then reinstates drug-seeking (Crombag et al., 2002; Fuchs et al., 2005).

A series of projections, primarily involving DA and Glu, from the VTA, basolateral amygdala (BLA), dmPFC, and NAc core, appear to be the primary pathways mediating conditioned-cued reinstatement (See, 2005). Understanding the neurocircuitry of cue-induced reinstatement may help to elucidate the neuroanatomical and neurochemical substrates of craving that drug addicts experience when confronted with cocaine paraphernalia such as syringes, needles, smoking pipes, etc. (O'Brien & Gardner, 2005).

In summary, although the neurocircuitries involved in drug-, cue-, and stress-induced reinstatement are distinct in a number of aspects, the cumulative findings indicate that projections from the VTA (all forms of reinstatement), limbic regions of the BLA (cue reinstatement), and the central amygdala, bed nucleus of the stria terminalis, and NAc shell (stress reinstatement) converge on motor pathways involving glutamatergic projection from the dmPFC to NAc core that represents a ‘final common pathway’ for all three types of instigating factors in relapse (Feltenstein & See, 2008; Kalivas & McFarland, 2003; Shaham et al., 2003). Moreover, enhanced synaptic release of Glu from terminals of prefrontal cortex neurons following all three triggering factors provokes reinstatement of drug-seeking (Knackstedt & Kalivas, 2009). Thus, pharmacological modulation of such substrates may yield potentially useful therapeutic modalities.

2.3. Validity of the reinstatement model to assess relapse in human

The most important question in interpreting the data from preclinical models is whether these data are of relevance to the understanding of human addiction and relapse. In this section, we summarize the criterion validity and construct validity of the reinstatement model.

2.3.1. Criterion validity—Criterion validity (or predictive validity) refers to the extent to which laboratory animal behavior induced by an experimental manipulation predicts human behavior induced by a similar event in the modeled condition. This level of validity is usually in reference to a model's ability to identify drugs with potential therapeutic value in humans (Geyer & Markou, 1995; Markou et al., 1993; Sarter & Bruno, 2002; Willner, 1984). Criterion validity of the reinstatement model is supported by evidence that reinstatement in laboratory animals (See, 2002; Shaham et al., 2003; Stewart et al., 2000; Weiss, 2005) can be triggered by conditions reported to provoke drug craving and relapse in human such as a drug (de Wit, 1996), drug-associated cues (Carter & Tiffany, 1999; Childress et al., 1993), or stress (Sinha, 2001).

A growing body of retrospective clinical evidence suggests the similarity of triggering factors of relapse between species. However, prospective studies and clinical trials that have tested effective medications in the reinstatement model are few in number (McKay et al., 2006). While addiction scientists generally agree that the reinstatement model has adequate criterion validity (Epstein et al., 2006), opinions differ concerning the model's ability to

identify drugs with potential therapeutic value in humans (Katz & Higgins, 2003; O'Brien & Gardner, 2005). It is important to note that very few studies have used designs comparable to those of reinstatement experiments, in which the clinical trial would enroll participants who are already abstinent or extinguished. The reason may be that abstinence requires expensive and often unavailable hospitalizations and human extinction (often referred to as exposure therapy) is frequently ineffective in substance users (Conklin & Tiffany, 2002). The main outcome measure in such trials would be propensity to undergo a specific type of relapse (e.g., relapse induced by stress or cues). Instead, the most commonly targeted outcome in clinical studies is reduction in ongoing drug intake or subjective effects of the drug (Vocci & Ling, 2005). Therefore, medication effects in most of these studies may be more related to the assessment of criterion validity of the drug self-administration procedure (Mello & Negus, 1996), rather than the reinstatement procedure. However, the pharmacological criterion validity of the reinstatement model appears promising in the cases of alcohol, heroin, and nicotine (Epstein et al., 2006). As we will discuss later, clinical trials have been conducted specifically to test medications (e.g., naltrexone and acamprosate) for relapse prevention in abstinent alcoholics (Latt et al., 2002; Tempesta et al., 2000). Drugs that modulate opioid function, specifically naltrexone (Comer et al., 2006), methadone (Leri et al., 2004), and buprenorphine (Sorge et al., 2005) showed promising results for prevention of opioid relapse. In the case of nicotine addiction, early studies demonstrated effectiveness of a cannabinoid CB1 antagonist (rimonabant) and a partial nicotinic receptor agonist (varenicline) to prevent relapse in abstinent smokers (Fagerstrom & Balfour, 2006; Spiller et al., 2009). However, as for cocaine or other psychostimulants, it has not yet been established that this model provides a useful screen for relapse-prevention medication, since potential medications identified in reinstatement studies have never been assessed in clinical trials designed to assess relapse prevention in abstinent humans.

2.3.2. Construct validity—Construct validity is defined by similarity in the mechanisms underlying behavior in the model and the modeled human condition (Epstein et al., 2006; Sarter & Bruno, 2002). Diverse opinions exist regarding the necessity of construct validity (Geyer & Markou, 1995; Sarter & Bruno, 2002). Despite reasonable homology between brain regions required for reinstatement in rats and brain regions activated during drug craving in human laboratory studies, the construct validity of the reinstatement model has not yet been truly established. This limitation is largely due to the lack of relevant clinical data. The problem for a model possessing criterion, but limited construct validity, is that the model may identify the right medications “for the wrong reasons” and will fail to identify medications with novel mechanisms of action (Russell, 1964; Sarter & Bruno, 2002). Although construct validity is desirable, almost none of the currently used animal models of neuropsychiatric diseases meet criteria for construct validity and uncertain construct validity is inevitable for any model of a psychiatric disorder with unknown etiology (Geyer & Markou, 1995; Willner, 1984). In conclusion, until clinical and preclinical databases are more comparable, criticisms of the reinstatement model's presumed shortcomings for construct validity remain premature.

2.3.3. Screening treatment medication—Although concerns about the face and construct validity of the reinstatement model of relapse are clearly important, these issues may not be the first priority from a clinical point of view. Clinicians are interested in finding viable and effective treatments for addiction and are therefore more concerned about the treatment screening ability of a model. Thus, appropriate studies to elucidate the criterion validity of the model, especially in the case of psychostimulants, are of more urgent attention. This approach may be criticized for being too myopic, for if a model has predictive validity without construct validity, it may screen some of the “right medications for the wrong reasons” and thus miss other potential medications with novel mechanisms of

action (Sarter & Bruno, 2002). However, as no medications currently exist for the prevention of relapse to psychostimulants, finding even one medication would be a significant treatment advance. Another concern about medication screening is the likelihood of obtaining a high rate of false positives, medications that appear promising when screened, but then fail in clinical trials. So far, the reinstatement model in animals has generated a large and growing body of basic science data on pharmacological interventions that prevent reinstatement of drug-seeking. However, clinical trials homologous to the reinstatement model are rare, especially in the case of psychostimulant addiction. A clinical trial with homology to the reinstatement model would enroll former substance users who are currently abstinent and would assess propensity to lapse or relapse. Clinical trials following such a protocol are rare, difficult to conduct, and the few that do exist have usually tested medications never tested in animal models of relapse. Therefore, while of clear concern, it remains premature to criticize the reinstatement model for generating false positives.

The closest points of homology between preclinical and clinical work in addictive disorders can be found in the alcohol literature. As already mentioned, naltrexone has been shown to block reinstatement of alcohol-seeking in rats (Le et al., 1999; Volpicelli, 1995) and also prevent relapse in alcoholics (Latt et al., 2002; Streeton & Whelan, 2001). The alcohol literature includes a few promising relapse-prevention clinical trials using acamprosate (Sass et al., 1996; Tempesta et al., 2000), which has been screened (with positive results) in the alcohol-deprivation model in rodents (Holter et al., 1997; Spanagel et al., 1996). However, acamprosate failed to reduce drinking behavior in a recent large clinical trial (Anton et al., 2006). On the other hand, some drugs have been shown to block reinstatement of alcohol-seeking in rodent models, but fail to prevent relapse in humans. For instance, fluoxetine blocked reinstatement of alcohol-seeking behavior in rats (Le et al., 1999), but failed to prevent relapse in alcoholics (Kranzler et al., 1995). One explanation for the negative findings with fluoxetine could be that the drug blocked only one particular subtype of reinstatement (stress-induced reinstatement) and the outcome measures in the clinical trial did not specifically include stress-induced relapse. Thus, specificity of reinstatement-blocking medications and the multifactorial nature of relapse suggest the necessity of targeted medications or even polypharmacy therapy for relapse prevention.

Further examination of both the preclinical and clinical data revealed some additional overlaps between animal models of relapse and human clinical studies, although the drug administration schedules differ. For example, the DA D1 receptor antagonists ABT-431 (Self et al., 2000) or SCH 39166 (ecopipam) (Ciccocioppo et al., 2001; Khroyan et al., 2000) blocked reinstatement of cocaine-seeking, and each of these drugs has been tested in human laboratory studies. Acute ABT-431 administration decreased subjective effects of acute cocaine and drug craving in a laboratory setting (Haney et al., 1999). However, administration of ABT-431 in a chronic, rather than acute schedule led to more potent blockade of reinstatement in rats (Self et al., 2000). On the other hand, both acute (Romach et al., 1999) and chronic (Haney et al., 2001) ecopipam administration reduced craving for cocaine in humans. However, a recent large multi-center phase III trial failed to show efficacy for ecopipam (personal communication from Robert Malcolm). Although acute ecopipam blocked reinstatement of cocaine-seeking in monkeys (Khroyan et al., 2000), no existing studies have used chronic treatment in an animal model.

If we further consider clinical trials that did not directly examine relapse prevention, some encouraging overlaps can be found between preclinical and clinical data. For example, the GABA_B receptor agonist, baclofen, blocked cocaine-primed reinstatement of cocaine-seeking in rats (Campbell et al., 1999) and decreased cocaine craving and use in outpatients (Ling et al., 1998). Another example is the partial opioid receptor agonist, buprenorphine, which attenuated drug-primed reinstatement of cocaine-seeking in rats (Comer et al., 1993),

as well as exhibiting promising results in reducing cocaine use in opiate-cocaine co-dependent addicts (Compton et al., 1995; Montoya et al., 2004; Schottenfeld et al., 1997). In addition, preclinical investigators have recently evaluated the effects of compounds previously investigated in clinical studies (i.e., “back translation”). Vigabatrin (gamma-vinyl GABA) increased abstinence rates in cocaine or methamphetamine addicts (Brodie et al., 2003; Brodie et al., 2005), and congruent animal data showed that vigabatrin reduced cocaine-induced reinstatement of drug-seeking in rats (Filip et al., 2007c; Peng et al., 2008a). Tiagabine, another GABA mimetic agent that showed some promise in clinical trials in cocaine-opiate co-dependent addicts (Gonzalez et al., 2007; Gonzalez et al., 2003), modestly reduced cocaine-primed reinstatement of drug-seeking in rats (Filip & Frankowska, 2007).

3. Drugs tested as anti-relapse medications in animal models

Over the past several years, a growing number of investigations have assessed the effects of different drugs on reinstatement of drug-seeking behavior using self-administration and relapse paradigms. One broad approach has been the determination of the neurocircuitry underlying various types of reinstatement to drug-seeking as produced by cues, stress, or drugs. Therefore, these studies have examined the effects of direct pharmacological interventions in specific brain regions (usually localized receptor antagonism or inhibition) on drug-taking and drug-seeking. Other studies have adopted approaches to screen potential medications that may block the acquisition, maintenance, or reinstatement of drug-taking and drug-seeking. Since relapse prevention is the most difficult and critical part of addiction treatment, animal model studies of possible anti-relapse medications will continue to be a major focus of preclinical research. At the current time, most previous studies in animal models have focused on cocaine self-administration and relapse. Although some studies have been carried out in primates, most of the existing data comes from studies in rats. We have summarized the studies that have evaluated potential medications for relapse to cocaine-seeking in tables 1 and 2, categorized based on their mechanisms of action. Table 1 includes the studies that have assessed systemic administration of monoaminergic drugs on reinstatement of cocaine-seeking, which includes drugs with primary receptor selectivity for central DA, serotonin, and/or norepinephrine systems. Table 2 summarizes results from other classes of drugs, including compounds that act on Glu, GABA, opioid, cannabinoid, and other neurotransmitters or neuromodulators. As seen in tables 1 and 2, the most commonly studied drugs to date act on DA, Glu, or serotonin systems. Drugs were administered systemically via different routes of administration (i.p., s.c., and p.o.). In a few studies, drug treatment was chronic (e.g., daily) or via a minipump infusion. Moreover, in few cases, discrepancies exist in the results of different studies conducted on the same drug that could be due to different dosage, pretreatment timing, and/or route of administration. In addition to cocaine studies, a few studies have assessed the effects of various drugs on the reinstatement of methamphetamine-seeking, and these are summarized in table 3.

It is noteworthy that most of the existing studies on putative anti-relapse medications have only evaluated the effects of acute drug administration on different forms of reinstatement. Only a few available studies have administered drugs in a chronic regimen during the period of cocaine self-administration or prior to reinstatement. The use of repeated drug administration provides a much more homologous approach, as treatment regimens in humans almost always continue for multiple days or even more prolonged time periods. In a few preclinical studies, drugs were chronically administered before each self-administration session and acutely on reinstatement tests with different results. For example, acute administration of acamprosate blocked both cocaine- and cue- induced reinstatement; however, chronic daily administration of acamprosate prior to each self-administration session had no effect on cocaine intake (Bowers et al., 2007). In another study, adenosine agonists exerted inhibitory effects on drug-taking during self-administration, but facilitated

the reinstatement of cocaine-seeking (Knapp et al., 2001). These results likely relate to the differences in the neurocircuitry underlying self-administration, extinction, and reinstatement. Some recent studies have tested repeated drug administration prior to reinstatement testing. Gonzalez-Cuevas and colleagues (2007) administered a cannabinoid agonist (WIN 55,212-2) subchronically during abstinence and observed enhanced context- and cue-induced reinstatement of cocaine-seeking with higher doses, but no effect with lower doses. In addition, chronic fluoxetine treatment during abstinence attenuated cue-, but not cocaine-induced reinstatement of cocaine-seeking (Baker et al., 2001). Moreover, rats maintained chronically on methadone (Leri et al., 2004) or buprenorphine (Sorge et al., 2005) showed reductions in both heroin- and cocaine-induced reinstatement of drug-seeking. Finally, chronic N-acetylcysteine administration during daily extinction sessions led to enduring inhibition of cue- and heroin-induced reinstatement of heroin-seeking (Zhou & Kalivas, 2008). Future testing and development of anti-relapse medications will require careful assessment of chronic dosing regimens at various timepoints and for various forms of relapse.

4. Drugs tested for the treatment of psychostimulant addiction in humans

Currently, no medications have been approved by the Food and Drug Administration for the treatment of psychostimulant addiction. Several clinical studies have been conducted on possible medications that might be efficacious in the treatment of cocaine/methamphetamine addiction. Table 4 summarizes compounds that have been administered in controlled clinical trials of cocaine and methamphetamine addiction. Some of these drugs are still under investigation, including modafinil (Dackis et al., 2005), disulfiram (Carroll et al., 2004), topiramate (Kampman et al., 2004), and several others. Here, we briefly describe results from some of the drugs that have been recently tested.

Studies in animals have consistently shown that enhancement of GABA activity reduces cocaine self-administration (Filip et al., 2007c; Peng et al., 2008a). As mentioned above, preliminary results from clinical trials using baclofen, a GABA_B agonist, and topiramate, which activates GABA_A receptors, have shown some success in reducing cocaine use in human subjects (Shoptaw et al., 2003). Moreover, a clinical laboratory study showed that baclofen reduced cocaine self-administration in non-opioid dependent, non-treatment-seeking cocaine addicts (Haney et al., 2006). However, baclofen did not help to initiate abstinence in heavy cocaine dependents in a recent clinical trial (Kahn et al., 2009). Topiramate was shown to reduce cocaine use and increase negative urine tests in an open label (Johnson, 2005), and a controlled clinical trial (Kampman et al., 2004). In addition, vigabatrin, an inhibitor of GABA transaminase, showed promising effects in three open label studies of cocaine- and/or methamphetamine-dependent outpatients (Brodie et al., 2003; Brodie et al., 2005; Fechtner et al., 2006). Controlled clinical trials are underway to further evaluate the effects of vigabatrin (Brodie et al., 2005). It should be noted that while visual safety for short term use in cocaine addicts is established (Fechtner et al., 2006), peripheral field damage with long term use is possible (The Royal College of Ophthalmology, 2008). While facilitation of GABA activity shows evidence for reducing cocaine use, it is interesting to note that tiagabine, which blocks presynaptic release of GABA, also decreased cocaine use and increased abstinence rate in two controlled clinical trials (Gonzalez et al., 2007; Gonzalez et al., 2003).

Several recent studies have tested various dopaminergic agents in the treatment of psychostimulant addiction. Bupropion, a nonselective DA reuptake inhibitor, showed variable effects in two different controlled trials in cocaine-opiate dependent individuals (Margolin et al., 1995; Poling et al., 2006). DA precursor treatment via L-dopa/carbidopa combination failed to reduce cocaine use or craving in three randomized, double-blind trials

(Mooney et al., 2007; Shoptaw et al., 2005), but showed some promising effects in combination with behavioral therapy (Schmitz et al., 2008). Several researchers have also evaluated the effects of second generation antipsychotic drugs on cocaine use and craving. Although risperidone and olanzapine reduced cocaine euphoria or cue-induced cocaine craving in human laboratory studies (Smelson et al., 2004; Smelson et al., 2006), they failed to reduce cocaine use in controlled clinical trials (Grabowski et al., 2004; Kampman et al., 2003; Reid et al., 2005). Aripiprazole is a novel antipsychotic drug that acts as a partial agonist at both DA D₂ and 5HT_{1A} receptors. We recently showed that acute aripiprazole blocked both cocaine- and cue-induced reinstatement of cocaine-seeking in rats (Feltenstein et al., 2007). In addition, aripiprazole has shown initial promising effects in reducing drug craving (Beresford et al., 2005; Vorspan et al., 2008) and clinical trials are currently underway to further examine its effectiveness. As noted in table 1, DA D₁-like receptor agonists attenuated both cocaine- and cue-induced reinstatement in rat models (Alleweireldt et al., 2002; Self et al., 2000; Spealman et al., 1999). One of these agonists (DAS-431, also called adrogolide) is under investigation in cocaine dependent subjects (Heidbreder & Hagan, 2005).

Another broad approach for psychostimulant addiction has been the evaluation of drugs with some similar pharmacological properties as abused psychostimulants to suppress withdrawal symptoms and prevent relapse (i.e., “agonist replacement therapy”). Methylphenidate is an approved medication for the treatment of attention deficit hyperactivity disorder that blocks catecholamine reuptake. Methylphenidate showed some beneficial effects in reducing cocaine use only in cocaine dependent patients with comorbid attention deficit hyperactivity disorder (Levin et al., 2007). As noted in table 4, disulfiram, a DA metabolism inhibitor, has been reported to reduce cocaine use in cocaine addicts with or without concurrent alcohol or opiate dependence (Carroll et al., 2004; Carroll et al., 1998; George et al., 2000; Petrakis et al., 2000). However, disulfiram also enhances cardiovascular responses to cocaine and thus produces cardiovascular side effects if combined with cocaine, although this risk may be less than originally estimated (Malcolm et al., 2008). Another recent treatment approach involves modafinil, which possesses stimulant-like activity and a complex pharmacodynamic profile that involves enhanced Glu activity (Dackis et al., 2005). As noted in table 4, modafinil has been reported to reduce cocaine use in comparison with placebo (Dackis et al., 2005). However, a recently completed multi-site, controlled clinical trial revealed that this effect is only significant in patients without alcohol dependence (Elkashef & Vocci, 2007). On the other hand, in one human laboratory study, pre-treatment with modafinil decreased cocaine discrimination (Malcolm et al., 2006). A more recent study found a reduction in cocaine self-administration in nontreatment-seeking cocaine-dependent individuals after modafinil treatment (Hart et al., 2008). In addition, dextroamphetamine treatment decreased cocaine use in cocaine- or cocaine/heroin-dependent subjects (Grabowski et al., 2004; Shearer et al., 2003). Finally, oral formulations of cocaine have been shown to decrease the subjective and physiological responses to cocaine (Walsh et al., 2000).

In addition to primarily targeting psychostimulant addiction, a few compounds have also been tested in patients with codependency to both cocaine and opiates. The opioid partial agonist, buprenorphine, has been found to reduce cocaine self-administration in monkeys (Mello & Negus, 2007) and decreased the use of opiates and cocaine in opiate-cocaine dependent individuals (Montoya et al., 2004). Another example is desipramine, a tricyclic antidepressant that reduced cocaine use in opiate-cocaine co-dependent patients maintained on buprenorphine (Kosten et al., 2003).

A somewhat different approach has been the development of vaccines that target cocaine, methamphetamine, nicotine, phencyclidine, or morphine (Orson et al., 2008). Vaccines act

by producing antibodies that bind to the drug during subsequent exposures and thereby block or reduce the rate of drug entry into the CNS. Animal studies have shown that conjugate vaccines produce an adequate amount of antibody and can inhibit both reinstatement and locomotor activity after re-exposure to drug (Carrera et al., 2000; Norman et al., 2009). In human studies, TA-CD vaccine (cholera toxin B conjugated cocaine preparation) significantly reduced cocaine effects during human laboratory trials and decreased cocaine use in outpatients, while concurrently exhibiting good immunogenicity, safety, and efficacy (Orson et al., 2008). Moreover, early preclinical studies of methamphetamine are underway and have demonstrated various effects on methamphetamine self-administration in rats (Duryee et al., 2009; McMillan et al., 2004; Orson et al., 2008).

In summary, although none of the drugs mentioned above has yet been approved for the treatment of psychostimulant addiction, several of these compounds have shown initial encouraging results in controlled clinical trials. Some of these drugs ameliorate withdrawal symptoms and reduce cocaine reinforcement, thus appearing to be better candidates for abstinence initiation (e.g., modafinil and bupropion). Other drugs (particularly GABA enhancing agents such as topiramate and vigabatrin) may increase unpleasant side effects and/or reduce cocaine reinforcement and craving. Such compounds may act more effectively for relapse prevention. Given the relatively limited data on all of these compounds, and significant side effects for some, more thorough assessments will be required to identify the best possible candidates for wider application in treatment.

In addition to drugs with published preliminary data on clinical efficacy, several classes of compounds identified in reinstatement studies could provide promising clinical leads. As noted in tables 1 and 2, examples are DA D3 antagonists, CRF1 receptor antagonists, mGluR2/3 receptor agonists, mGluR5 antagonists, N-acetylcysteine, and dual dopamine/serotonin releasers such as PAL-278 (Rothman et al., 2008).

5. Summary and conclusions

Although drug addiction exacts great human and financial costs on society, the development of adequate pharmacotherapies for addiction has not yet been successful. In fact, from a pharmacotherapy development perspective, addiction has been largely neglected by the pharmaceutical industry. Treatment of relapse to drug-seeking and drug-taking is considered the most difficult and critical part of treating addictive behaviors. In this review, we focused on animal models of relapse that may be applied for the testing of novel anti-relapse medications and we summarized the growing body of pharmacological interventions that have shown some promise in treating relapse in psychostimulant addiction. In assessing the summated literature on the overlap of available preclinical and clinical data, it is apparent that while a scientific framework has been established, a great deal of careful preclinical and clinical studies will need to be conducted to further assess potential medications.

As mentioned earlier, notable gaps exist between the approaches used in animal models of relapse and clinical research on relapse prevention. Although there has been a rapid increase in the number of recent reinstatement studies that focused on identifying potential pharmacological treatments for relapse prevention, preclinical scientists need to systematically direct new efforts toward medication screening. Several procedural issues must be considered in future studies. As alluded to earlier in this review, most preclinical investigations have only tested acute drug administration. However, in almost all clinical psychiatric situations, medications are chronically administered. Therefore, future animal studies should strive to assess the effects of both acute and repeated administration of the test drug. Greater consideration of pharmacokinetic issues is also warranted, given the

importance of pharmacokinetics in clinical pharmacology. Continued refinement of reinstatement procedures will also improve the relevance of animal model studies for application in the clinical arena. For example, prior studies on stress-induced reinstatement in animals have mostly used intermittent footshock (Erb et al., 1996; McFarland et al., 2004; Piazza & Le Moal, 1998) as a stressor, while human studies have used image-guided scripts or social stress tests (Li et al., 2005; Sinha et al., 2005). We and others have found that stress-inducing compounds, notably yohimbine, can readily reinstate drug-seeking in rats and monkeys (Feltenstein & See, 2006; Lee et al., 2004; Shepard et al., 2004). This same experimental approach can be used in humans to provoke craving states in addicts (Stine et al., 2001), and we are currently using this “cross-species” approach in parallel studies to test anti-relapse medications for stress-activated relapse and craving in both rats and humans.

For the development of clinical studies, clinicians could make better use of the preclinical data as a guide for future drug targets. Clinical trials could also be designed with greater homology to preclinical experiments in terms of study design, specificity of outcome measures, and inclusion of abstinent former users. Despite resource limitations, more clinical trials of stimulant addiction treatment should start with baseline abstinence. Medications could be selected based on promising findings in preclinical screening studies and the propensity to relapse should be measured in real-time. These approaches will also help to elucidate predictive validity of this model. Since different medications may block only a specific form of reinstatement of drug-seeking in animal models, clinicians should also consider polypharmacy as a viable approach.

In conclusion, numerous drugs have shown promise in preclinical models of relapse that warrant further clinical evaluations as such compounds become available. New advances in our understanding of the neurobiology of addiction and relapse will continue to guide the most promising areas for future drug development. Furthermore, it seems that the gap between basic and clinical research in terms of anti-relapse medication development could be narrowed by an increase in translational research and increased crosstalk between preclinical and clinical investigators. The fruit of such endeavors would be the identification and application of truly successful pharmacotherapies for addictive disorders.

Acknowledgments

Research by the authors has been supported by NIH grants DA10462, DA15369, DA16511, DA21690, and DA22658. The authors also would like to thank Robert Malcolm, Carmela Reichel, and Pouya Tahsili-Fahadan for their invaluable comments on earlier versions of this review.

Abbreviations

BLA	basolateral amygdala
CPP	conditioned place preference
dmPFC	dorsomedial prefrontal cortex
DA	dopamine
GABA	γ -Aminobutyric acid
Glu	glutamate
NAc	nucleus accumbens
VTa	ventral tegmental area

References

- Acosta JJ, Boynton FA, Kirschner KF, Neisewander JL. Stimulation of 5-HT1B receptors decreases cocaine- and sucrose-seeking behavior. *Pharmacol Biochem Behav* 2005;80(2):297–307. [PubMed: 15680183]
- Aguilar MA, Rodriguez-Arias M, Minarro J. Neurobiological mechanisms of the reinstatement of drug-conditioned place preference. *Brain Res Rev* 2009;59(2):253–277. [PubMed: 18762212]
- Alleweireldt AT, Kirschner KF, Blake CB, Neisewander JL. D1-receptor drugs and cocaine-seeking behavior: investigation of receptor mediation and behavioral disruption in rats. *Psychopharmacology (Berl)* 2003;168(1-2):109–117. [PubMed: 12520312]
- Alleweireldt AT, Weber SM, Kirschner KF, Bullock BL, Neisewander JL. Blockade or stimulation of D1 dopamine receptors attenuates cue reinstatement of extinguished cocaine-seeking behavior in rats. *Psychopharmacology (Berl)* 2002;159(3):284–293. [PubMed: 11862361]
- Anggadiredja K, Nakamichi M, Hiranita T, Tanaka H, Shoyama Y, Watanabe S, et al. Endocannabinoid system modulates relapse to methamphetamine seeking: possible mediation by the arachidonic acid cascade. *Neuropsychopharmacology* 2004a;29(8):1470–1478. [PubMed: 15085091]
- Anggadiredja K, Sakimura K, Hiranita T, Yamamoto T. Naltrexone attenuates cue- but not drug-induced methamphetamine seeking: a possible mechanism for the dissociation of primary and secondary reward. *Brain Res* 2004b;1021(2):272–276. [PubMed: 15342276]
- Anker JJ, Holtz NA, Zlebnik N, Carroll ME. Effects of allopregnanolone on the reinstatement of cocaine-seeking behavior in male and female rats. *Psychopharmacology (Berl)* 2009;203(1):63–72. [PubMed: 18998113]
- Anker JJ, Larson EB, Gliddon LA, Carroll ME. Effects of progesterone on the reinstatement of cocaine-seeking behavior in female rats. *Exp Clin Psychopharmacol* 2007;15(5):472–480. [PubMed: 17924781]
- Antkiewicz-Michaluk L, Filip M, Michaluk J, Romanska I, Przegalinski E, Vetulani J. An endogenous neuroprotectant substance, 1-methyl-1,2,3,4-tetrahydroisoquinoline (1MeTIQ), prevents the behavioral and neurochemical effects of cocaine reinstatement in drug-dependent rats. *J Neural Transm* 2007;114(3):307–317. [PubMed: 16897599]
- Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. *JAMA* 2006;295(17):2003–2017. [PubMed: 16670409]
- Backstrom P, Hyttia P. Ionotropic and metabotropic glutamate receptor antagonism attenuates cue-induced cocaine seeking. *Neuropsychopharmacology* 2006;31(4):778–786. [PubMed: 16123768]
- Baker DA, McFarland K, Lake RW, Shen H, Tang XC, Toda S, et al. Neuroadaptations in cystine-glutamate exchange underlie cocaine relapse. *Nat Neurosci* 2003a;6(7):743–749. [PubMed: 12778052]
- Baker DA, McFarland K, Lake RW, Shen H, Toda S, Kalivas PW. N-acetyl cysteine-induced blockade of cocaine-induced reinstatement. *Ann N Y Acad Sci* 2003b;1003:349–351. [PubMed: 14684458]
- Baker DA, Tran-Nguyen TL, Fuchs RA, Neisewander JL. Influence of individual differences and chronic fluoxetine treatment on cocaine-seeking behavior in rats. *Psychopharmacology (Berl)* 2001;155(1):18–26. [PubMed: 11374332]
- Beardsley PM, Howard JL, Shelton KL, Carroll FI. Differential effects of the novel kappa opioid receptor antagonist, JDTic, on reinstatement of cocaine-seeking induced by footshock stressors vs cocaine primes and its antidepressant-like effects in rats. *Psychopharmacology (Berl)* 2005;183(1):118–126. [PubMed: 16184376]
- Beresford TP, Clapp L, Martin B, Wiberg JL, Alfors J, Beresford HF. Aripiprazole in schizophrenia with cocaine dependence: a pilot study. *J Clin Psychopharmacol* 2005;25(4):363–366. [PubMed: 16012280]
- 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(1):37–44. [PubMed: 10821207]

- Boctor SY, Martinez JL Jr, Koek W, France CP. The cannabinoid CB1 receptor antagonist AM251 does not modify methamphetamine reinstatement of responding. *Eur J Pharmacol* 2007;571(1):39–43. [PubMed: 17628534]
- Bouton M, Swartzentruber D. Sources of relapse after extinction in Pavlovian and instrumental learning. *Clin Psychol Rev* 1991;11:18.
- Boutrel B, Kenny PJ, Specio SE, Martin-Fardon R, Markou A, Koob GF, et al. Role for hypocretin in mediating stress-induced reinstatement of cocaine-seeking behavior. *Proc Natl Acad Sci U S A* 2005;102(52):19168–19173. [PubMed: 16357203]
- Bowers MS, Chen BT, Chou JK, Osborne MP, Gass JT, See RE, et al. Acamprosate attenuates cocaine- and cue-induced reinstatement of cocaine-seeking behavior in rats. *Psychopharmacology (Berl)* 2007;195(3):397–406. [PubMed: 17764007]
- Brimijoin S, Gao Y, Anker JJ, Gliddon LA, Lafleur D, Shah R, et al. A Cocaine Hydrolase Engineered from Human Butyrylcholinesterase Selectively Blocks Cocaine Toxicity and Reinstatement of Drug Seeking in Rats. *Neuropsychopharmacology*. 2008
- Brodie JD, Figueroa E, Dewey SL. Treating cocaine addiction: from preclinical to clinical trial experience with gamma-vinyl GABA. *Synapse* 2003;50(3):261–265. [PubMed: 14515344]
- Brodie JD, Figueroa E, Laska EM, Dewey SL. Safety and efficacy of gamma-vinyl GABA (GVG) for the treatment of methamphetamine and/or cocaine addiction. *Synapse* 2005;55(2):122–125. [PubMed: 15543630]
- Burattini C, Burbassi S, Aicardi G, Cervo L. Effects of naltrexone on cocaine- and sucrose-seeking behaviour in response to associated stimuli in rats. *Int J Neuropsychopharmacol* 2008;11(1):103–109. [PubMed: 17335644]
- Burbassi S, Cervo L. Stimulation of serotonin_{2C} receptors influences cocaine-seeking behavior in response to drug-associated stimuli in rats. *Psychopharmacology (Berl)* 2008;196(1):15–27. [PubMed: 17899022]
- Burmeister JJ, Lungren EM, Kirschner KF, Neisewander JL. Differential roles of 5-HT receptor subtypes in cue and cocaine reinstatement of cocaine-seeking behavior in rats. *Neuropsychopharmacology* 2004;29(4):660–668. [PubMed: 14627998]
- Burmeister JJ, Lungren EM, Neisewander JL. Effects of fluoxetine and d-fenfluramine on cocaine-seeking behavior in rats. *Psychopharmacology (Berl)* 2003;168(1-2):146–154. [PubMed: 12529808]
- Caine SB, Koob GF. Modulation of cocaine self-administration in the rat through D-3 dopamine receptors. *Science* 1993;260(5115):1814–1816. [PubMed: 8099761]
- Campbell UC, Lac ST, Carroll ME. Effects of baclofen on maintenance and reinstatement of intravenous cocaine self-administration in rats. *Psychopharmacology (Berl)* 1999;143(2):209–214. [PubMed: 10326784]
- Carrera MR, Ashley JA, Zhou B, Wirsching P, Koob GF, Janda KD. Cocaine vaccines: antibody protection against relapse in a rat model. *Proc Natl Acad Sci U S A* 2000;97(11):6202–6206. [PubMed: 10823960]
- Carroll KM, Fenton LR, Ball SA, Nich C, Frankforter TL, Shi J, et al. Efficacy of disulfiram and cognitive behavior therapy in cocaine-dependent outpatients: a randomized placebo-controlled trial. *Arch Gen Psychiatry* 2004;61(3):264–272. [PubMed: 14993114]
- Carroll KM, Nich C, Ball SA, McCance E, Rounsavile BJ. Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram. *Addiction* 1998;93(5):713–727. [PubMed: 9692270]
- Carter BL, Tiffany ST. Meta-analysis of cue-reactivity in addiction research. *Addiction* 1999;94(3):327–340. [PubMed: 10605857]
- Cervo L, Carnovali F, Stark JA, Mennini T. Cocaine-seeking behavior in response to drug-associated stimuli in rats: involvement of D3 and D2 dopamine receptors. *Neuropsychopharmacology* 2003;28(6):1150–1159. [PubMed: 12700684]
- Cervo L, Cocco A, Petrella C, Heidbreder CA. Selective antagonism at dopamine D3 receptors attenuates cocaine-seeking behaviour in the rat. *Int J Neuropsychopharmacol* 2007;10(2):167–181. [PubMed: 16426478]

- Childress AR, Hole AV, Ehrman RN, Robbins SJ, McLellan AT, O'Brien CP. Cue reactivity and cue reactivity interventions in drug dependence. *NIDA Res Monogr* 1993;137:73–95. [PubMed: 8289929]
- 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 U S A* 2001;98(4):1976–1981. [PubMed: 11172061]
- Collins RJ, Weeks JR, Cooper MM, Good PI, Russell RR. Prediction of abuse liability of drugs using IV self-administration by rats. *Psychopharmacology (Berl)* 1984;82(1-2):6–13. [PubMed: 6141585]
- Comer SD, Lac ST, Curtis LK, Carroll ME. Effects of buprenorphine and naltrexone on reinstatement of cocaine-reinforced responding in rats. *J Pharmacol Exp Ther* 1993;267(3):1470–1477. [PubMed: 7903391]
- Comer SD, Sullivan MA, Yu E, Rothenberg JL, Kleber HD, Kampman K, et al. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. *Arch Gen Psychiatry* 2006;63(2):210–218. [PubMed: 16461865]
- 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(3):97–114. [PubMed: 8555282]
- Conklin CA, Tiffany ST. Applying extinction research and theory to cue-exposure addiction treatments. *Addiction* 2002;97(2):155–167. [PubMed: 11860387]
- Crombag HS, Grimm JW, Shaham Y. Effect of dopamine receptor antagonists on renewal of cocaine seeking by reexposure to drug-associated contextual cues. *Neuropsychopharmacology* 2002;27(6):1006–1015. [PubMed: 12464457]
- Dackis CA, Kampman KM, Lynch KG, Pettinati HM, O'Brien CP. A double-blind, placebo-controlled trial of modafinil for cocaine dependence. *Neuropsychopharmacology* 2005;30(1):205–211. [PubMed: 15525998]
- Davidson C, Gopalan R, Ahn C, Chen Q, Mannelli P, Patkar AA, et al. Reduction in methamphetamine induced sensitization and reinstatement after combined pergolide plus ondansetron treatment during withdrawal. *Eur J Pharmacol* 2007;565(1-3):113–118. [PubMed: 17408614]
- de Wit H. Priming Effects With Drugs and Other Reinforcers. *Experimental and Clinical Psychopharmacology* 1996;4:5–11.
- de Wit H, Stewart J. Reinstatement of cocaine-reinforced responding in the rat. *Psychopharmacology (Berl)* 1981;75(2):134–143. [PubMed: 6798603]
- Deroche-Gamonet V, Belin D, Piazza PV. Evidence for addiction-like behavior in the rat. *Science* 2004;305(5686):1014–1017. [PubMed: 15310906]
- Doron R, Fridman L, Gispán-Herman I, Maayan R, Weizman A, Yadid G. DHEA, a neurosteroid, decreases cocaine self-administration and reinstatement of cocaine-seeking behavior in rats. *Neuropsychopharmacology* 2006;31(10):2231–2236. [PubMed: 16421515]
- Duryee MJ, Bevins RA, Reichel CM, Murray JE, Dong Y, Thiele GM, et al. Immune responses to methamphetamine by active immunization with peptide-based, molecular adjuvant-containing vaccines. *Vaccine* 2009;27(22):2981–2988. [PubMed: 19428909]
- Elkashef, A.; Vocci, J. Promising medications for the treatment of cocaine addiction; Paper presented at the American Psychiatric Association Annual Meeting; San Diego, CA. 2007.
- Elkashef AM, Rawson RA, Anderson AL, Li SH, Holmes T, Smith EV, et al. Bupropion for the treatment of methamphetamine dependence. *Neuropsychopharmacology* 2008;33(5):1162–1170. [PubMed: 17581531]
- Epstein DH, Preston KL, Stewart J, Shaham Y. Toward a model of drug relapse: an assessment of the validity of the reinstatement procedure. *Psychopharmacology (Berl)* 2006;189(1):1–16. [PubMed: 17019567]
- Erb S, Hitchcott PK, Rajabi H, Mueller D, Shaham Y, Stewart J. Alpha-2 adrenergic receptor agonists block stress-induced reinstatement of cocaine seeking. *Neuropsychopharmacology* 2000;23(2):138–150. [PubMed: 10882840]
- Erb S, Shaham Y, Stewart J. Stress reinstates cocaine-seeking behavior after prolonged extinction and a drug-free period. *Psychopharmacology (Berl)* 1996;128(4):408–412. [PubMed: 8986011]

- 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(14):5529–5536. [PubMed: 9651233]
- Fagerstrom K, Balfour DJ. Neuropharmacology and potential efficacy of new treatments for tobacco dependence. *Expert Opin Investig Drugs* 2006;15(2):107–116.
- Fechtner RD, Khouri AS, Figueroa E, Ramirez M, Federico M, Dewey SL, et al. Short-term treatment of cocaine and/or methamphetamine abuse with vigabatrin: ocular safety pilot results. *Arch Ophthalmol* 2006;124(9):1257–1262. [PubMed: 16966620]
- Feltenstein MW, Altar CA, See REAC. Aripiprazole blocks reinstatement of cocaine seeking in an animal model of relapse. *Biol Psychiatry* 2007;61(5):582–590. [PubMed: 16806092]
- Feltenstein MW, Byrd EA, Henderson AR, See RE. Attenuation of cocaine-seeking by progesterone treatment in female rats. *Psychoneuroendocrinology* 2009;34(3):343–352. [PubMed: 18977603]
- Feltenstein MW, See RE. Potentiation of cue-induced reinstatement of cocaine-seeking in rats by the anxiogenic drug yohimbine. *Behav Brain Res* 2006;174(1):1–8. [PubMed: 16920204]
- Feltenstein MW, See RE. The neurocircuitry of addiction: an overview. *Br J Pharmacol* 2008;154(2):261–274. [PubMed: 18311189]
- Filip M. Role of serotonin (5-HT)₂ receptors in cocaine self-administration and seeking behavior in rats. *Pharmacol Rep* 2005;57(1):35–46. [PubMed: 15849375]
- Filip M, Antkiewicz-Michaluk L, Zaniowska M, Frankowska M, Golda A, Vetulani J, et al. Effects of 1-methyl-1,2,3,4-tetrahydroisoquinoline on the behavioral effects of cocaine in rats. *J Physiol Pharmacol* 2007a;58(4):625–639. [PubMed: 18195477]
- Filip M, Frankowska M. Effects of GABA(B) receptor agents on cocaine priming, discrete contextual cue and food induced relapses. *Eur J Pharmacol* 2007;571(2-3):166–173. [PubMed: 17610868]
- Filip M, Frankowska M, Przegalinski E. Effects of GABA(B) receptor antagonist, agonists and allosteric positive modulator on the cocaine-induced self-administration and drug discrimination. *Eur J Pharmacol* 2007b;574(2-3):148–157. [PubMed: 17698060]
- Filip M, Frankowska M, Zaniowska M, Golda A, Przegalinski E, Vetulani J. Diverse effects of GABA-mimetic drugs on cocaine-evoked self-administration and discriminative stimulus effects in rats. *Psychopharmacology (Berl)* 2007c;192(1):17–26. [PubMed: 17256126]
- Filip M, Golda A, Zaniowska M, McCreary AC, Nowak E, Kolasiewicz W, et al. Involvement of cannabinoid CB1 receptors in drug addiction: effects of rimonabant on behavioral responses induced by cocaine. *Pharmacol Rep* 2006;58(6):806–819. [PubMed: 17220538]
- Fletcher PJ, Grottick AJ, Higgins GA. Differential effects of the 5-HT(2A) receptor antagonist M100907 and the 5-HT(2C) receptor antagonist SB242084 on cocaine-induced locomotor activity, cocaine self-administration and cocaine-induced reinstatement of responding. *Neuropsychopharmacology* 2002;27(4):576–586. [PubMed: 12377394]
- Fletcher PJ, Rizos Z, Sinyard J, Tampakeras M, Higgins GA. The 5-HT_{2C} receptor agonist Ro60-0175 reduces cocaine self-administration and reinstatement induced by the stressor yohimbine, and contextual cues. *Neuropsychopharmacology* 2008;33(6):1402–1412. [PubMed: 17653111]
- Foltin RW, Haney M. Conditioned effects of environmental stimuli paired with smoked cocaine in humans. *Psychopharmacology (Berl)* 2000;149(1):24–33. [PubMed: 10789879]
- Fuchs RA, Branham RK, See RE. Different neural substrates mediate cocaine seeking after abstinence versus extinction training: a critical role for the dorsolateral caudate-putamen. *J Neurosci* 2006;26(13):3584–3588. [PubMed: 16571766]
- Fuchs RA, Evans KA, Ledford CC, Parker MP, Case JM, Mehta RH, et al. The role of the dorsomedial prefrontal cortex, basolateral amygdala, and dorsal hippocampus in contextual reinstatement of cocaine seeking in rats. *Neuropsychopharmacology* 2005;30(2):296–309. [PubMed: 15483559]
- Gal K, Gyertyan I. Dopamine D3 as well as D2 receptor ligands attenuate the cue-induced cocaine-seeking in a relapse model in rats. *Drug Alcohol Depend* 2006;81(1):63–70. [PubMed: 16005579]
- Gass JT, Osborne MP, Watson NL, Brown JL, Olive MF. mGluR5 antagonism attenuates methamphetamine reinforcement and prevents reinstatement of methamphetamine-seeking behavior in rats. *Neuropsychopharmacology* 2009;34(4):820–833. [PubMed: 18800068]

- George TP, Chawarski MC, Pakes J, Carroll KM, Kosten TR, Schottenfeld RS. Disulfiram versus placebo for cocaine dependence in buprenorphine-maintained subjects: a preliminary trial. *Biol Psychiatry* 2000;47(12):1080–1086. [PubMed: 10862808]
- Gerber GJ, Stretch R. Drug-induced reinstatement of extinguished self-administration behavior in monkeys. *Pharmacol Biochem Behav* 1975;3(6):1055–1061. [PubMed: 817297]
- Gerrits MA, Kuzmin AV, van Ree JM. Reinstatement of cocaine-seeking behavior in rats is attenuated following repeated treatment with the opioid receptor antagonist naltrexone. *Eur Neuropsychopharmacol* 2005;15(3):297–303. [PubMed: 15820419]
- Geyer, M.; Markou, A. Animal models of psychiatric disorders. In: FE Bloom, DK., editor. *Psychopharmacology: the fourth generation of progress*. Raven, New York: 1995. p. 787-798.
- Gilbert JG, Newman AH, Gardner EL, Ashby CR Jr, Heidbreder CA, Pak AC, et al. Acute administration of SB-277011A, NGB 2904, or BP 897 inhibits cocaine cue-induced reinstatement of drug-seeking behavior in rats: role of dopamine D3 receptors. *Synapse* 2005;57(1):17–28. [PubMed: 15858839]
- Goeders NE, Clampitt DM. Potential role for the hypothalamo-pituitary-adrenal axis in the conditioned reinforcer-induced reinstatement of extinguished cocaine seeking in rats. *Psychopharmacology (Berl)* 2002;161(3):222–232. [PubMed: 12021825]
- Goeders NE, Clampitt DM, Keller C, Sharma M, Guerin GF. Alprazolam and oxazepam block the cue-induced reinstatement of extinguished cocaine seeking in rats. *Psychopharmacology (Berl)* 2009;201(4):581–588. [PubMed: 18797849]
- Gonzalez-Cuevas G, Aujla H, Martin-Fardon R, Lopez-Moreno JA, Navarro M, Weiss F. Subchronic cannabinoid agonist (WIN 55,212-2) treatment during cocaine abstinence alters subsequent cocaine seeking behavior. *Neuropsychopharmacology* 2007;32(11):2260–2266. [PubMed: 17392740]
- Gonzalez G, Desai R, Sofuoglu M, Poling J, Oliveto A, Gonsai K, et al. Clinical efficacy of gabapentin versus tiagabine for reducing cocaine use among cocaine dependent methadone-treated patients. *Drug Alcohol Depend* 2007;87(1):1–9. [PubMed: 16930857]
- Gonzalez G, Sevarino K, Sofuoglu M, Poling J, Oliveto A, Gonsai K, et al. Tiagabine increases cocaine-free urines in cocaine-dependent methadone-treated patients: results of a randomized pilot study. *Addiction* 2003;98(11):1625–1632. [PubMed: 14616189]
- Grabowski J, Rhoades H, Stotts A, Cowan K, Kopecky C, Dougherty A, et al. Agonist-like or antagonist-like treatment for cocaine dependence with methadone for heroin dependence: two double-blind randomized clinical trials. *Neuropsychopharmacology* 2004;29(5):969–981. [PubMed: 15039761]
- Gyertyan I, Kiss B, Gal K, Laszlovszky I, Horvath A, Gemesi LI, et al. Effects of RGH-237 [N-{4-[4-(3-aminocarbonyl-phenyl)-piperazin-1-yl]-butyl}-4-bromo-benzamide], an orally active, selective dopamine D(3) receptor partial agonist in animal models of cocaine abuse. *J Pharmacol Exp Ther* 2007;320(3):1268–1278. [PubMed: 17170312]
- 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 (Berl)* 1999;143(1):102–110. [PubMed: 10227086]
- Haney M, Hart CL, Foltin RW. Effects of baclofen on cocaine self-administration: opioid- and nonopioid-dependent volunteers. *Neuropsychopharmacology* 2006;31(8):1814–1821. [PubMed: 16407903]
- Haney M, Ward AS, Foltin RW, Fischman MW. Effects of ecopipam, a selective dopamine D1 antagonist, on smoked cocaine self-administration by humans. *Psychopharmacology (Berl)* 2001;155(4):330–337. [PubMed: 11441422]
- Harrod SB, Dwoskin LP, Green TA, Gehrke BJ, Bardo MT. Lobeline does not serve as a reinforcer in rats. *Psychopharmacology (Berl)* 2003;165(4):397–404. [PubMed: 12459929]
- Hart CL, Haney M, Vosburg SK, Rubin E, Foltin RW. Smoked cocaine self-administration is decreased by modafinil. *Neuropsychopharmacology* 2008;33(4):761–768. [PubMed: 17568397]
- Heidbreder CA, Hagan JJ. Novel pharmacotherapeutic approaches for the treatment of drug addiction and craving. *Curr Opin Pharmacol* 2005;5(1):107–118. [PubMed: 15661634]

- Highfield D, Yap J, Grimm JW, 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(3):320–331. [PubMed: 11522461]
- Hiranita T, Anggadiredja K, Fujisaki C, Watanabe S, Yamamoto T. Nicotine attenuates relapse to methamphetamine-seeking behavior (craving) in rats. *Ann N Y Acad Sci* 2004;1025:504–507. [PubMed: 15542755]
- Hiranita T, Nawata Y, Sakimura K, Anggadiredja K, Yamamoto T. Suppression of methamphetamine-seeking behavior by nicotinic agonists. *Proc Natl Acad Sci U S A* 2006;103(22):8523–8527. [PubMed: 16717181]
- 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(5):862–868. [PubMed: 9267536]
- Hyman SE, Malenka RC. Addiction and the brain: the neurobiology of compulsion and its persistence. *Nat Rev Neurosci* 2001;2(10):695–703. [PubMed: 11584307]
- Jaffe JH. Trivializing dependence. *Br J Addict* 1990;85(11):1425–1427. discussion 1429–1431. [PubMed: 2285838]
- Jaffe JH, Cascella NG, Kumor KM, Sherer MA. Cocaine-induced cocaine craving. *Psychopharmacology (Berl)* 1989;97(1):59–64. [PubMed: 2496428]
- Johnson BA. Recent advances in the development of treatments for alcohol and cocaine dependence: focus on topiramate and other modulators of GABA or glutamate function. *CNS Drugs* 2005;19(10):873–896. [PubMed: 16185095]
- Kahn R, Biswas K, Childress AR, Shoptaw S, Fudala PJ, Gorgon L, et al. Multi-center trial of baclofen for abstinence initiation in severe cocaine-dependent individuals. *Drug Alcohol Depend* 2009;103(1-2):59–64. [PubMed: 19414226]
- Kalivas PW, McFarland K. Brain circuitry and the reinstatement of cocaine-seeking behavior. *Psychopharmacology (Berl)* 2003;168(1-2):44–56. [PubMed: 12652346]
- Kalivas PW, O'Brien C. Drug addiction as a pathology of staged neuroplasticity. *Neuropsychopharmacology* 2008;33(1):166–180. [PubMed: 17805308]
- Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. *Am J Psychiatry* 2005;162(8):1403–1413. [PubMed: 16055761]
- Kampman KM, Dackis C, Lynch KG, Pettinati H, Tirado C, Gariti P, et al. A double-blind, placebo-controlled trial of amantadine, propranolol, and their combination for the treatment of cocaine dependence in patients with severe cocaine withdrawal symptoms. *Drug Alcohol Depend* 2006;85(2):129–137. [PubMed: 16697124]
- Kampman KM, Pettinati H, Lynch KG, Dackis C, Sparkman T, Weigley C, et al. A pilot trial of topiramate for the treatment of cocaine dependence. *Drug Alcohol Depend* 2004;75(3):233–240. [PubMed: 15283944]
- Kampman KM, Pettinati H, Lynch KG, Sparkman T, O'Brien CP. A pilot trial of olanzapine for the treatment of cocaine dependence. *Drug Alcohol Depend* 2003;70(3):265–273. [PubMed: 12757964]
- Kampman KM, Volpicelli JR, Mulvaney F, Alterman AI, Cornish J, Gariti P, et al. Effectiveness of propranolol for cocaine dependence treatment may depend on cocaine withdrawal symptom severity. *Drug Alcohol Depend* 2001;63(1):69–78. [PubMed: 11297832]
- Katz JL, Higgins ST. The validity of the reinstatement model of craving and relapse to drug use. *Psychopharmacology (Berl)* 2003;168(1-2):21–30. [PubMed: 12695875]
- 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(2):680–687. [PubMed: 10900248]
- Knackstedt LA, Kalivas PW. Glutamate and reinstatement. *Curr Opin Pharmacol* 2009;9(1):59–64. [PubMed: 19157986]
- Knapp CM, Foye MM, Cottam N, Ciraulo DA, Kornetsky C. Adenosine agonists CGS 21680 and NECA inhibit the initiation of cocaine self-administration. *Pharmacol Biochem Behav* 2001;68(4):797–803. [PubMed: 11526979]

- Koob GF, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology* 2001;24(2):97–129. [PubMed: 11120394]
- Kosten T, Oliveto A, Feingold A, Poling J, Sevarino K, McCance-Katz E, et al. Desipramine and contingency management for cocaine and opiate dependence in buprenorphine maintained patients. *Drug Alcohol Depend* 2003;70(3):315–325. [PubMed: 12757969]
- Kranzler HR, Burleson JA, Korner P, Del Boca FK, Bohn MJ, Brown J, et al. Placebo-controlled trial of fluoxetine as an adjunct to relapse prevention in alcoholics. *Am J Psychiatry* 1995;152(3):391–397. [PubMed: 7864265]
- Kupferschmidt DA, Tribe E, Erb S. Effects of repeated yohimbine on the extinction and reinstatement of cocaine seeking. *Pharmacol Biochem Behav* 2009;91(3):473–480. [PubMed: 18824018]
- Larson EB, Carroll ME. Estrogen receptor beta, but not alpha, mediates estrogen's effect on cocaine-induced reinstatement of extinguished cocaine-seeking behavior in ovariectomized female rats. *Neuropsychopharmacology* 2007;32(6):1334–1345. [PubMed: 17133264]
- Larson EB, Roth ME, Anker JJ, Carroll ME. Effect of short- vs. long-term estrogen on reinstatement of cocaine-seeking behavior in female rats. *Pharmacol Biochem Behav* 2005;82(1):98–108. [PubMed: 16111740]
- 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 Aust* 2002;176(11):530–534. [PubMed: 12064984]
- Le AD, Poulos CX, Harding S, Watchus J, Juzysch 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(3):435–444. [PubMed: 10457541]
- LeBlanc AE, Kalant H, Gibbins RJ, Berman ND. Acquisition and loss of tolerance to ethanol by the rat. *J Pharmacol Exp Ther* 1969;168(2):244–250. [PubMed: 5803308]
- Lee B, Tiefenbacher S, Platt DM, Spealman RD. Pharmacological blockade of alpha2-adrenoceptors induces reinstatement of cocaine-seeking behavior in squirrel monkeys. *Neuropsychopharmacology* 2004;29(4):686–693. [PubMed: 14872205]
- Leri F, Tremblay A, Sorge RE, Stewart J. Methadone maintenance reduces heroin- and cocaine-induced relapse without affecting stress-induced relapse in a rodent model of poly-drug use. *Neuropsychopharmacology* 2004;29(7):1312–1320. [PubMed: 15039768]
- Levin FR, Evans SM, Brooks DJ, Garawi F. Treatment of cocaine dependent treatment seekers with adult ADHD: double-blind comparison of methylphenidate and placebo. *Drug Alcohol Depend* 2007;87(1):20–29. [PubMed: 16930863]
- Li CS, Kosten TR, Sinha R. Sex differences in brain activation during stress imagery in abstinent cocaine users: a functional magnetic resonance imaging study. *Biol Psychiatry* 2005;57(5):487–494. [PubMed: 15737663]
- Ling W, Shoptaw S, Majewska D. Baclofen as a cocaine anti-craving medication: a preliminary clinical study. *Neuropsychopharmacology* 1998;18(5):403–404. [PubMed: 9536455]
- Lu L, Liu D, Ceng X, Ma L. Differential roles of corticotropin-releasing factor receptor subtypes 1 and 2 in opiate withdrawal and in relapse to opiate dependence. *Eur J Neurosci* 2000;12(12):4398–4404. [PubMed: 11122350]
- Malcolm R, Olive MF, Lechner W. The safety of disulfiram for the treatment of alcohol and cocaine dependence in randomized clinical trials: guidance for clinical practice. *Expert Opin Drug Saf* 2008;7(4):459–472. [PubMed: 18613809]
- Malcolm R, Swayngim K, Donovan JL, DeVane CL, Elkashef A, Chiang N, et al. Modafinil and cocaine interactions. *Am J Drug Alcohol Abuse* 2006;32(4):577–587. [PubMed: 17127546]
- 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 (Berl)* 1999a;142(4):399–407. [PubMed: 10229065]
- Mantsch JR, Goeders NE. Ketoconazole does not block cocaine discrimination or the cocaine-induced reinstatement of cocaine-seeking behavior. *Pharmacol Biochem Behav* 1999b;64(1):65–73. [PubMed: 10494999]

- Mantsch JR, Li SJ, Risinger R, Awad S, Katz E, Baker DA, et al. Levo-tetrahydropalmatine attenuates cocaine self-administration and cocaine-induced reinstatement in rats. *Psychopharmacology (Berl)* 2007;192(4):581–591. [PubMed: 17361394]
- Madayag A, Lobner D, Kau KS, Mantsch JR, Abdulhameed O, Hearing M, et al. Repeated N-acetylcysteine administration alters plasticity-dependent effects of cocaine. *J Neurosci* 2007;27(51):13968–13976. [PubMed: 18094234]
- Margolin A, Kosten TR, Avants SK, Wilkins J, Ling W, Beckson M, et al. A multicenter trial of bupropion for cocaine dependence in methadone-maintained patients. *Drug Alcohol Depend* 1995;40(2):125–131. [PubMed: 8745134]
- Markou A, Weiss F, Gold LH, Caine SB, Schulteis G, Koob GF. Animal models of drug craving. *Psychopharmacology (Berl)* 1993;112(2-3):163–182. [PubMed: 7871016]
- Martell BA, Mitchell E, Poling J, Gonsai K, Kosten TR. Vaccine pharmacotherapy for the treatment of cocaine dependence. *Biol Psychiatry* 2005;58(2):158–164. [PubMed: 16038686]
- Martin-Fardon R, Baptista MA, Dayas CV, Weiss F. Dissociation of the effects of MTEP on conditioned reinstatement and reinforcement: Comparison between cocaine and a conventional reinforcer. *J Pharmacol Exp Ther*. 2009
- Martin-Fardon R, Ciccocioppo R, Massi M, Weiss F. Nociceptin prevents stress-induced ethanol- but not cocaine-seeking behavior in rats. *Neuroreport* 2000;11(9):1939–1943. [PubMed: 10884047]
- Martin-Fardon R, Maurice T, Aujla H, Bowen WD, Weiss F. Differential effects of sigma1 receptor blockade on self-administration and conditioned reinstatement motivated by cocaine vs natural reward. *Neuropsychopharmacology* 2007;32(9):1967–1973. [PubMed: 17268407]
- McFarland K, Davidge SB, Lapish CC, Kalivas PW. Limbic and motor circuitry underlying footshock-induced reinstatement of cocaine-seeking behavior. *J Neurosci* 2004;24(7):1551–1560. [PubMed: 14973230]
- McFarland K, Kalivas PW. The circuitry mediating cocaine-induced reinstatement of drug-seeking behavior. *J Neurosci* 2001;21(21):8655–8663. [PubMed: 11606653]
- McKay JR, Franklin TR, Patapis N, Lynch KG. Conceptual, methodological, and analytical issues in the study of relapse. *Clin Psychol Rev* 2006;26(2):109–127. [PubMed: 16371242]
- McMillan DE, Hardwick WC, Li M, Gunnell MG, Carroll FI, Abraham P, et al. Effects of murine-derived anti-methamphetamine monoclonal antibodies on (+)-methamphetamine self-administration in the rat. *J Pharmacol Exp Ther* 2004;309(3):1248–1255. [PubMed: 14993256]
- Mello NK, Negus SS. Preclinical evaluation of pharmacotherapies for treatment of cocaine and opioid abuse using drug self-administration procedures. *Neuropsychopharmacology* 1996;14(6):375–424. [PubMed: 8726752]
- Mello NK, Negus SS. Effects of d-amphetamine and buprenorphine combinations on speedball (cocaine+heroin) self-administration by rhesus monkeys. *Neuropsychopharmacology* 2007;32(9):1985–1994. [PubMed: 17228335]
- Milivojevic N, Krisch I, Sket D, Zivin M. The dopamine D1 receptor agonist and D2 receptor antagonist LEK-8829 attenuates reinstatement of cocaine-seeking in rats. [Drug]. *Naunyn Schmiedeberg Arch Pharmacol* 2004;369(6):576–582. [PubMed: 15138661]
- Moeller FG, Schmitz JM, Steinberg JL, Green CM, Reist C, Lai LY, et al. Citalopram combined with behavioral therapy reduces cocaine use: a double-blind, placebo-controlled trial. *Am J Drug Alcohol Abuse* 2007;33(3):367–378. [PubMed: 17613964]
- Moffett MC, Goeders NE. CP-154,526, a CRF type-1 receptor antagonist, attenuates the cue- and methamphetamine-induced reinstatement of extinguished methamphetamine-seeking behavior in rats. *Psychopharmacology (Berl)* 2007;190(2):171–180. [PubMed: 17119930]
- Montoya ID, Gorelick DA, Preston KL, Schroeder JR, Umbricht A, Cheskin LJ, et al. Randomized trial of buprenorphine for treatment of concurrent opiate and cocaine dependence. *Clin Pharmacol Ther* 2004;75(1):34–48. [PubMed: 14749690]
- Mooney ME, Schmitz JM, Moeller FG, Grabowski J. Safety, tolerability and efficacy of levodopa-carbidopa treatment for cocaine dependence: two double-blind, randomized, clinical trials. *Drug Alcohol Depend* 2007;88(2-3):214–223. [PubMed: 17134849]

- Moore RY, Bloom FE. Central catecholamine neuron systems: anatomy and physiology of the norepinephrine and epinephrine systems. *Annu Rev Neurosci* 1979;2:113–168. [PubMed: 231924]
- Moran MM, McFarland K, Melendez RI, Kalivas PW, Seamans JK. Cystine/glutamate exchange regulates metabotropic glutamate receptor presynaptic inhibition of excitatory transmission and vulnerability to cocaine seeking. *J Neurosci* 2005;25(27):6389–6393. [PubMed: 16000629]
- Mueller D, Stewart J. Cocaine-induced conditioned place preference: reinstatement by priming injections of cocaine after extinction. *Behav Brain Res* 2000;115(1):39–47. [PubMed: 10996406]
- Neisewander JL, Acosta JI. Stimulation of 5-HT_{2C} receptors attenuates cue and cocaine-primed reinstatement of cocaine-seeking behavior in rats. *Behav Pharmacol* 2007;18(8):791–800. [PubMed: 17989517]
- Nestler EJ. From neurobiology to treatment: progress against addiction. *Nat Neurosci* 2002;5(Suppl): 1076–1079. [PubMed: 12403990]
- Nic Dhonnchadha BA, Fox RG, Stutz SJ, Rice KC, Cunningham KA. Blockade of the serotonin 5-HT_{2A} receptor suppresses cue-evoked reinstatement of cocaine-seeking behavior in a rat self-administration model. *Behav Neurosci* 2009;123(2):382–396. [PubMed: 19331461]
- Norman AB, Norman MK, Buesing WR, Tabet MR, Tsibulsky VL, Ball WJ. The effect of a chimeric human/murine anti-cocaine monoclonal antibody on cocaine self-administration in rats. *J Pharmacol Exp Ther* 2009;328(3):873–881. [PubMed: 19088302]
- O'Brien, C.; Parker, K. Drug addiction and drug abuse. In: Brunton, JLL., editor. *Goodman and Gilman's the pharmacological basis of therapeutics*. 11th ed.. McGraw-Hill; New York: 2006. p. 607–627.
- O'Brien CP. A range of research-based pharmacotherapies for addiction. *Science* 1997;278(5335):66–70. [PubMed: 9311929]
- O'Brien CP. Review. Evidence-based treatments of addiction. *Philos Trans R Soc Lond B Biol Sci* 2008;363(1507):3277–3286. [PubMed: 18640914]
- O'Brien CP, Gardner EL. Critical assessment of how to study addiction and its treatment: human and non-human animal models. *Pharmacol Ther* 2005;108(1):18–58. [PubMed: 16183393]
- O'Brien CP, McLellan AT. Myths about the treatment of addiction. *Lancet* 1996;347(8996):237–240. [PubMed: 8551886]
- Orsini C, Izzo E, Koob GF, Pulvirenti L. Blockade of nitric oxide synthesis reduces responding for cocaine self-administration during extinction and reinstatement. *Brain Res* 2002;925(2):133–140. [PubMed: 11792361]
- Orson FM, Kinsey BM, Singh RA, Wu Y, Gardner T, Kosten TR. Substance abuse vaccines. *Ann N Y Acad Sci* 2008;1141:257–269. [PubMed: 18991962]
- Peng XQ, Ashby CR Jr, Spiller K, Li X, Li J, Thomasson N, et al. The preferential dopamine D(3) receptor antagonist S33138 inhibits cocaine reward and cocaine-triggered relapse to drug-seeking behavior in rats. *Neuropharmacology* 2009;56(4):752–760. [PubMed: 19136017]
- Peng XQ, Li X, Gilbert JG, Pak AC, Ashby CR Jr, Brodie JD, et al. Gamma-vinyl GABA inhibits cocaine-triggered reinstatement of drug-seeking behavior in rats by a non-dopaminergic mechanism. *Drug Alcohol Depend* 2008a;97(3):216–225. [PubMed: 18063319]
- Peng XQ, Li X, Li J, Ramachandran PV, Gagare PD, Pratihara D, et al. Effects of gabapentin on cocaine self-administration, cocaine-triggered relapse and cocaine-enhanced nucleus accumbens dopamine in rats. *Drug Alcohol Depend* 2008b;97(3):207–215. [PubMed: 18065162]
- Peters J, Kalivas PW. The group II metabotropic glutamate receptor agonist, LY379268, inhibits both cocaine- and food-seeking behavior in rats. *Psychopharmacology (Berl)*. 2006
- Petrakis IL, Carroll KM, Nich C, Gordon LT, McCance-Katz EF, Frankforter T, et al. Disulfiram treatment for cocaine dependence in methadone-maintained opioid addicts. *Addiction* 2000;95(2):219–228. [PubMed: 10723850]
- Piazza PV, Le Moal M. The role of stress in drug self-administration. *Trends Pharmacol Sci* 1998;19(2):67–74. [PubMed: 9550944]
- Placenza FM, Vaccarino FJ, Fletcher PJ, Erb S. Activation of central neurokinin-1 receptors induces reinstatement of cocaine-seeking behavior. *Neurosci Lett* 2005;390(1):42–47. [PubMed: 16125318]

- Poling J, Oliveto A, Petry N, Sofuoglu M, Gonsai K, Gonzalez G, et al. Six-month trial of bupropion with contingency management for cocaine dependence in a methadone-maintained population. *Arch Gen Psychiatry* 2006;63(2):219–228. [PubMed: 16461866]
- Przegalinski E, Filip M, Frankowska M, Zaniowska M, Papla I. Effects of CP 154,526, a CRF1 receptor antagonist, on behavioral responses to cocaine in rats. *Neuropeptides* 2005;39(5):525–533. [PubMed: 16139885]
- Przegalinski E, Golda A, Filip M. Effects of serotonin (5-HT)(1B) receptor ligands on cocaine-seeking behavior in rats. *Pharmacol Rep* 2008;60(6):798–810. [PubMed: 19211971]
- Reid MS, Casadonte P, Baker S, Sanfilippo M, Braunstein D, Hitzemann R, et al. A placebo-controlled screening trial of olanzapine, valproate, and coenzyme Q10/L-carnitine for the treatment of cocaine dependence. *Addiction* 2005;100(Suppl 1):43–57. [PubMed: 15730349]
- Romach MK, Glue P, Kampman K, Kaplan HL, Somer GR, Poole S, et al. Attenuation of the euphoric effects of cocaine by the dopamine D1/D5 antagonist ecopipam (SCH 39166). *Arch Gen Psychiatry* 1999;56(12):1101–1106. [PubMed: 10591286]
- Rothman RB, Blough BE, Baumann MH. Dual dopamine/serotonin releasers: potential treatment agents for stimulant addiction. *Exp Clin Psychopharmacol* 2008;16(6):458–474. [PubMed: 19086767]
- Russell, R. Exploration from animals to man. In: Steinberg, A., editor. *Animal behavior and drug addiction*. Little; Boston: 1964. p. 410-418.
- Sarter, M.; Bruno, J. Animal models in biological psychiatry. In: D. h., H.; d. B., JA.; W., P., editors. *Biological Psychiatry*. Wiley and sons; Hoboken, NJ: 2002. p. 1-8.
- Sass H, Soyka M, Mann K, Zieglgansberger W. Relapse prevention by acamprosate. Results from a placebo-controlled study on alcohol dependence. *Arch Gen Psychiatry* 1996;53(8):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(2):363–369. [PubMed: 11124402]
- Schenk S, Gittings D. Effects of SCH 23390 and eticlopride on cocaine-seeking produced by cocaine and WIN 35,428 in rats. *Psychopharmacology (Berl)* 2003;168(1-2):118–123. [PubMed: 12420155]
- Schenk S, Partridge B, Shippenberg TS. U69593, a kappa-opioid agonist, decreases cocaine self-administration and decreases cocaine-produced drug-seeking. *Psychopharmacology (Berl)* 1999;144(4):339–346. [PubMed: 10435406]
- Schenk S, Partridge B, Shippenberg TS. Reinstatement of extinguished drug-taking behavior in rats: effect of the kappa-opioid receptor agonist, U69593. *Psychopharmacology (Berl)* 2000;151(1):85–90. [PubMed: 10958121]
- Schmitz JM, Mooney ME, Moeller FG, Stotts AL, Green C, Grabowski J. Levodopa pharmacotherapy for cocaine dependence: choosing the optimal behavioral therapy platform. *Drug Alcohol Depend* 2008;94(1-3):142–150. [PubMed: 18164144]
- Schottenfeld RS, Pakes JR, Oliveto A, Ziedonis D, Kosten TR. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Arch Gen Psychiatry* 1997;54(8):713–720. [PubMed: 9283506]
- See RE. Neural substrates of conditioned-cued relapse to drug-seeking behavior. *Pharmacol Biochem Behav* 2002;71(3):517–529. [PubMed: 11830186]
- See RE. Neural substrates of cocaine-cue associations that trigger relapse. *Eur J Pharmacol* 2005;526(1-3):140–146. [PubMed: 16253228]
- Self DW, Karanian DA, Spencer JJ. Effects of the novel D1 dopamine receptor agonist ABT-431 on cocaine self-administration and reinstatement. *Ann N Y Acad Sci* 2000;909:133–144. [PubMed: 10911927]
- Shaham Y, Erb S, Leung S, Buczek Y, Stewart J. CP-154,526, a selective, non-peptide antagonist of the corticotropin-releasing factor1 receptor attenuates stress-induced relapse to drug seeking in cocaine- and heroin-trained rats. *Psychopharmacology (Berl)* 1998;137(2):184–190. [PubMed: 9630005]

- Shaham Y, Erb S, Stewart J. Stress-induced relapse to heroin and cocaine seeking in rats: a review. *Brain Res Brain Res Rev* 2000;33(1):13–33. [PubMed: 10967352]
- Shaham Y, Highfield D, Delfs J, Leung S, Stewart J. Clonidine blocks stress-induced reinstatement of heroin seeking in rats: an effect independent of locus coeruleus noradrenergic neurons. *Eur J Neurosci* 2000;12(1):292–302. [PubMed: 10651884]
- Shaham Y, Shalev U, Lu L, De Wit H, Stewart J. The reinstatement model of drug relapse: history, methodology and major findings. *Psychopharmacology (Berl)* 2003;168(1-2):3–20. [PubMed: 12402102]
- Shalev U, Grimm JW, Shaham Y. Neurobiology of relapse to heroin and cocaine seeking: a review. *Pharmacol Rev* 2002;54(1):1–42. [PubMed: 11870259]
- Shalev U, Marinelli M, Baumann MH, Piazza PV, Shaham Y. The role of corticosterone in food deprivation-induced reinstatement of cocaine seeking in the rat. *Psychopharmacology (Berl)* 2003;168(1-2):170–176. [PubMed: 12845419]
- Shearer J, Wodak A, van Beek I, Mattick RP, Lewis J. Pilot randomized double blind placebo-controlled study of dexamphetamine for cocaine dependence. *Addiction* 2003;98(8):1137–1141. [PubMed: 12873248]
- Shepard JD, Bossert JM, Liu SY, Shaham Y. The anxiogenic drug yohimbine reinstates methamphetamine seeking in a rat model of drug relapse. *Biol Psychiatry* 2004;55(11):1082–1089. [PubMed: 15158427]
- Shiffman S. Relapse following smoking cessation: a situational analysis. *J Consult Clin Psychol* 1982;50(1):71–86. [PubMed: 7056922]
- Shiffman S, Hickcox M, Paty JA, Gnys M, Kassel JD, Richards TJ. Progression from a smoking lapse to relapse: prediction from abstinence violation effects, nicotine dependence, and lapse characteristics. *J Consult Clin Psychol* 1996;64(5):993–1002. [PubMed: 8916628]
- Shoptaw S, Watson DW, Reiber C, Rawson RA, Montgomery MA, Majewska MD, et al. Randomized controlled pilot trial of cabergoline, hydergine and levodopa/carbidopa: Los Angeles Cocaine Rapid Efficacy Screening Trial (CREST). *Addiction* 2005;100(Suppl 1):78–90. [PubMed: 15730352]
- Shoptaw S, Yang X, Rotheram-Fuller EJ, Hsieh YC, Kintaudi PC, Charuvastra VC, et al. Randomized placebo-controlled trial of baclofen for cocaine dependence: preliminary effects for individuals with chronic patterns of cocaine use. *J Clin Psychiatry* 2003;64(12):1440–1448. [PubMed: 14728105]
- Sinha R. How does stress increase risk of drug abuse and relapse? *Psychopharmacology (Berl)* 2001;158(4):343–359. [PubMed: 11797055]
- Sinha R, Catapano D, O'Malley S. Stress-induced craving and stress response in cocaine dependent individuals. *Psychopharmacology (Berl)* 1999;142(4):343–351. [PubMed: 10229058]
- Sinha R, Garcia M, Paliwal P, Kreek MJ, Rounsaville BJ. Stress-induced cocaine craving and hypothalamic-pituitary-adrenal responses are predictive of cocaine relapse outcomes. *Arch Gen Psychiatry* 2006;63(3):324–331. [PubMed: 16520439]
- Sinha R, Lacadie C, Skudlarski P, Fulbright RK, Rounsaville BJ, Kosten TR, et al. Neural activity associated with stress-induced cocaine craving: a functional magnetic resonance imaging study. *Psychopharmacology (Berl)* 2005;183(2):171–180. [PubMed: 16163517]
- Smelson DA, Williams J, Ziedonis D, Sussner BD, Losonczy MF, Engelhart C, et al. A double-blind placebo-controlled pilot study of risperidone for decreasing cue-elicited craving in recently withdrawn cocaine dependent patients. *J Subst Abuse Treat* 2004;27(1):45–49. [PubMed: 15223093]
- Smelson DA, Ziedonis D, Williams J, Losonczy MF, Steinberg ML, Kaune M. The efficacy of olanzapine for decreasing cue-elicited craving in individuals with schizophrenia and cocaine dependence: a preliminary report. *J Clin Psychopharmacol* 2006;26(1):9–12. [PubMed: 16415698]
- Sofuoglu M, Kosten TR. Emerging pharmacological strategies in the fight against cocaine addiction. *Expert Opin Emerg Drugs* 2006;11(1):91–98. [PubMed: 16503828]

- Sorge RE, Rajabi H, Stewart J. Rats maintained chronically on buprenorphine show reduced heroin and cocaine seeking in tests of extinction and drug-induced reinstatement. *Neuropsychopharmacology* 2005;30(9):1681–1692. [PubMed: 15798781]
- Spanagel R, Holter SM, Allingham K, Landgraf R, Zieglansberger W. Acamprosate and alcohol: I. Effects on alcohol intake following alcohol deprivation in the rat. *Eur J Pharmacol* 1996;305(1-3):39–44. [PubMed: 8813529]
- Spealman RD, Barrett-Larimore RL, Rowlett JK, Platt DM, Khroyan TV. Pharmacological and environmental determinants of relapse to cocaine-seeking behavior. *Pharmacol Biochem Behav* 1999;64(2):327–336. [PubMed: 10515309]
- Spiller K, Xi ZX, Li X, Ashby CR Jr, Callahan PM, Tehim A, et al. Varenicline attenuates nicotine-enhanced brain-stimulation reward by activation of $\alpha 4\beta 2$ nicotinic receptors in rats. *Neuropharmacology*. 2009
- Stewart D, Gossop M, Marsden J, Strang J. Variation between and within drug treatment modalities: data from the National Treatment Outcome Research Study (UK). *Eur Addict Res* 2000;6(3):106–114. [PubMed: 11060474]
- Stewart J. Reinstatement of heroin and cocaine self-administration behavior in the rat by intracerebral application of morphine in the ventral tegmental area. *Pharmacol Biochem Behav* 1984;20(6):917–923. [PubMed: 6463075]
- Stewart J, Vezina P. A comparison of the effects of intra-accumbens injections of amphetamine and morphine on reinstatement of heroin intravenous self-administration behavior. *Brain Res* 1988;457(2):287–294. [PubMed: 3219557]
- Stine SM, Grillon CG, Morgan CA 3rd, Kosten TR, Charney DS, Krystal JH. Methadone patients exhibit increased startle and cortisol response after intravenous yohimbine. *Psychopharmacology (Berl)* 2001;154(3):274–281. [PubMed: 11351934]
- Streeton C, Whelan G. Naltrexone, a relapse prevention maintenance treatment of alcohol dependence: a meta-analysis of randomized controlled trials. *Alcohol Alcohol* 2001;36(6):544–552. [PubMed: 11704620]
- 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 Alcohol* 2000;35(2):202–209. [PubMed: 10787398]
- The Royal College of Ophthalmologists. The Ocular Side-Effects of Vigabatrin (Sabril) Information and Guidance for Screening. The Royal College of Ophthalmologists; London: 2008.
- Torreghrossa MM, Kalivas PW. Neurotensin in the ventral pallidum increases extracellular gamma-aminobutyric acid and differentially affects cue- and cocaine-primed reinstatement. *J Pharmacol Exp Ther* 2008;325(2):556–566. [PubMed: 18252810]
- Tzschentke TM. Measuring reward with the conditioned place preference (CPP) paradigm: update of the last decade. *Addict Biol* 2007;12(3-4):227–462. [PubMed: 17678505]
- Vocci F, Ling W. Medications development: successes and challenges. *Pharmacol Ther* 2005;108(1):94–108. [PubMed: 16083966]
- Volpicelli JR. Naltrexone in alcohol dependence. *Lancet* 1995;346(8973):456. [PubMed: 7637475]
- Vorel SR, Ashby CR Jr, Paul M, Liu X, Hayes R, Hagan JJ, et al. Dopamine D3 receptor antagonism inhibits cocaine-seeking and cocaine-enhanced brain reward in rats. *J Neurosci* 2002;22(21):9595–9603. [PubMed: 12417684]
- Vorspan F, Bellais L, Keijzer L, Lepine JP. An open-label study of aripiprazole in nonschizophrenic crack-dependent patients. *J Clin Psychopharmacol* 2008;28(5):570–572. [PubMed: 18794657]
- Walsh SL, Haberny KA, Bigelow GE. Modulation of intravenous cocaine effects by chronic oral cocaine in humans. *Psychopharmacology (Berl)* 2000;150(4):361–373. [PubMed: 10958077]
- Wang B, Luo F, Zhang WT, Han JS. Stress or drug priming induces reinstatement of extinguished conditioned place preference. *Neuroreport* 2000;11(12):2781–2784. [PubMed: 10976962]
- Weiss F. Neurobiology of craving, conditioned reward and relapse. *Curr Opin Pharmacol* 2005;5(1):9–19. [PubMed: 15661620]
- Weiss F, Maldonado-Vlaar CS, Parsons LH, Kerr TM, Smith DL, Ben-Shahar O. Control of cocaine-seeking behavior by drug-associated stimuli in rats: effects on recovery of extinguished operant-

- responding and extracellular dopamine levels in amygdala and nucleus accumbens. *Proc Natl Acad Sci U S A* 2000;97(8):4321–4326. [PubMed: 10760299]
- Willner P. The validity of animal models of depression. *Psychopharmacology (Berl)* 1984;83(1):1–16. [PubMed: 6429692]
- Xi ZX, Gardner EL. Pharmacological actions of NGB 2904, a selective dopamine D3 receptor antagonist, in animal models of drug addiction. *CNS Drug Rev* 2007;13(2):240–259. [PubMed: 17627675]
- Xi ZX, Gilbert J, Campos AC, Kline N, Ashby CR Jr, Hagan JJ, et al. Blockade of mesolimbic dopamine D3 receptors inhibits stress-induced reinstatement of cocaine-seeking in rats. *Psychopharmacology (Berl)* 2004;176(1):57–65. [PubMed: 15083257]
- Xi ZX, Gilbert JG, Pak AC, Ashby CR Jr, Heidbreder CA, Gardner EL. Selective dopamine D3 receptor antagonism by SB-277011A attenuates cocaine reinforcement as assessed by progressive-ratio and variable-cost-variable-payoff fixed-ratio cocaine self-administration in rats. *Eur J Neurosci* 2005;21(12):3427–3438. [PubMed: 16026480]
- Xi ZX, Gilbert JG, Peng XQ, Pak AC, Li X, Gardner EL. Cannabinoid CB1 receptor antagonist AM251 inhibits cocaine-primed relapse in rats: role of glutamate in the nucleus accumbens. *J Neurosci* 2006a;26(33):8531–8536. [PubMed: 16914679]
- Xi ZX, Newman AH, Gilbert JG, Pak AC, Peng XQ, Ashby CR Jr, et al. The novel dopamine D3 receptor antagonist NGB 2904 inhibits cocaine's rewarding effects and cocaine-induced reinstatement of drug-seeking behavior in rats. *Neuropsychopharmacology* 2006b;31(7):1393–1405. [PubMed: 16205781]
- Xi ZX, Yang Z, Li SJ, Li X, Dillon C, Peng XQ, et al. Levo-tetrahydropalmatine inhibits cocaine's rewarding effects: experiments with self-administration and brain-stimulation reward in rats. *Neuropharmacology* 2007;53(6):771–782. [PubMed: 17888459]
- Zhang XY, Kosten TA. Prazosin, an alpha-1 adrenergic antagonist, reduces cocaine-induced reinstatement of drug-seeking. *Biol Psychiatry* 2005;57(10):1202–1204. [PubMed: 15866561]
- Zhou W, Kalivas PW. N-acetylcysteine reduces extinction responding and induces enduring reductions in cue- and heroin-induced drug-seeking. *Biol Psychiatry* 2008;63(3):338–340. [PubMed: 17719565]

Figure 1.

Experimental paradigm for reinstatement of drug-seeking behavior showing active (drug-paired) lever presses in representative phases of drug self-administration (acquisition and maintenance), extinction, and reinstatement test days (cue-induced, drug-induced, stress-induced). Animals undergo extinction sessions in between the reinstatement test.

Table 1

Effects of different systemic monoaminergic (dopamine, serotonin, norepinephrine) drugs on the reinstatement of cocaine-seeking in rats induced by cocaine, cue, stress, or context.

Class of drug	Drug	Route and dose	Effect	Reference
Dopamine	ABT-431 (D ₁ agonist)	1 or 3 mg/kg, s.c.	↓ cocaine	(Self et al., 2000)
	SKF-81297 (full D ₁ agonist)	3 mg/kg, s.c.	↓ cue, ↓ cocaine	(Alleweireldt et al., 2002, 2003)
	SKF-38393 (partial D ₁ agonist)	3 mg/kg, s.c.	↔ cue	(Alleweireldt et al., 2002)
	SCH-23390 (D ₁ antagonist)	10 µg/kg, s.c.	↓ cue	(Alleweireldt et al., 2002)
		5 or 10 µg/kg, s.c.	↓ context	(Crombag et al., 2002)
		1-10 µg/kg, s.c.	↔ cocaine	(Schenk & Gittings, 2003)
	LEK-8829 (D ₁ agonist /D ₂ antagonist)	0.1-1 mg/kg, i.v.	↓ cocaine	(Milivojevic et al., 2004)
	Eticlopride (D ₂ antagonist)	0.3 mg/kg, i.p.	↓ cocaine	(Schenk & Gittings, 2003)
	Raclopride (D ₂ antagonist)	0.1 or 0.3 mg/kg, s.c.	↓ cue	(Cervo et al., 2003)
		50 or 100 µg/kg, s.c.	↓ context	(Crombag et al., 2002)
	Haloperidol (preferential D ₂ antagonist)	0.2 mg/kg, p.o.	↓ cue	(Gal & Gyertyan, 2006)
	Aripiprazole (partial D ₂ agonist)	0.1-15 mg/kg, i.p.	↓ cue	(Feltenstein et al., 2007)
		0.25-15 mg/kg, i.p.	↓ cocaine	(Feltenstein et al., 2007)
	Levo-tetrahydropalmatine (l-THP) (D ₁ /D ₂ antagonist)	3.75 or 7.5 mg/kg, i.p.	↓ cocaine	(Mantsch et al., 2007)
		20 mg/kg, ip	↓ cocaine	(Xi et al., 2007)
	BP897 (D ₃ partial agonist/D ₂ antagonist)	1-3 mg/kg i.p.	↓ cue	(Cervo et al., 2003; Gal & Gyertyan, 2006; Gilbert et al., 2005)
	S33138 (partially selective D ₃ antagonist)	0.156-2.5 mg/kg, p.o.	↓ cocaine	(Peng et al., 2009)
	1-methyl-1,2,3,4-tetrahydroisoquinoline	50 mg/kg, i.p.	↓ cocaine	(Antkiewicz-Michaluk et al., 2007)
	RGH-237 (selective D ₃ partial agonist)	10 or 30 mg/kg, p.o.	↓ cue	(Gyertyan et al., 2007)
	7-OH-DPAT (D ₃ agonist)	0.1 or 0.3 mg/kg, i.p.	↓ cue	(Cervo et al., 2003)
		1 or 3 mg/kg, i.p.	↑ cue	(Cervo et al., 2003)
	SB-277011-A (selective D ₃ antagonist)	5-30 mg/kg, i.p. or p.o.	↓ cue	(Cervo et al., 2007; Gilbert et al., 2005; Gal & Gyertyan, 2006)
		3-24 mg/kg i.p.	↓ cocaine	(Vorel et al., 2002; Xi et al., 2005)
		3-12 mg/kg, ip	↓ stress (footshock)	(Xi et al., 2004)
	NGB 2904 (D ₃ antagonist)	0.1-5.0 mg/kg, i.p.	↓ cue	(Gilbert et al., 2005; Xi & Gardner, 2007)
			↓ cocaine	(Xi et al., 2006b; Xi & Gardner, 2007)
Serotonin	RU24969 (5-HT(1B/1A) receptor agonist)	1 or 3 mg/kg, s.c.	↓ cue, ↓ cocaine.	(Acosta et al., 2005)
	SB 216641 (5-HT(1B) receptor antagonists)	2.5-7.5 mg/kg, i.p.	↓ cue ↓ cocaine	(Przegalinski et al., 2008)
	WAY 100,635 (5-HT(1A) receptor antagonist)	0.1-1.0 mg/kg, s.c.	↔ cue	(Cervo et al., 2003; Burmeister et al., 2004)
		0.1-1.0 mg/kg, s.c.	↓ cocaine	(Schenk, 2000; Burmeister et al., 2004)

Class of drug	Drug	Route and dose	Effect	Reference
	GR 127935 (5-HT(1B) receptor antagonist)	2.5-10 mg/kg, s.c.	↓ cue ↓ cocaine	(Przegalinski et al., 2008)
	Ro 60-0175 (nonselective 5-HT(2B/C) agonist)	0.1-1 mg/kg, i.p.	↓ cue ↓ stress	(Burbassi & Cervo, 2008) (Fletcher et al., 2008)
		0.3-3 mg/kg, s.c.	↓ context	(Fletcher et al., 2008)
	SB 242,084 (5-HT(2C)-selective antagonist)	1.0 mg/kg, i.p.	↔ cue ↔ cocaine	(Burmeister et al., 2004)
	Ketanserin (5-HT(2A/C) antagonist)	10.0 mg/kg, i.p.	↓ cue ↔ cocaine	(Burmeister et al., 2004)
	M100907 (volinanserin) (selective 5-HT(2A) antagonist)	0.001-0.8 mg/kg, i.p.	↓ cue	(Nic Dhonnchadha et al., 2009)
	SR 46349B (5-HT(2A) receptor antagonist)	0.5-1 mg/kg, s.c.	↓ cue ↓ cocaine	(Filip, 2005)
	SDZ SER-082 (5-HT(2C) receptor antagonist)	0.25-1 mg/kg, i.p.	↔ cue ↔ cocaine	(Filip, 2005)
	M100907 (selective 5-HT(2A) receptor antagonist)	0.5 mg/kg, s.c.	↓ cocaine	(Fletcher et al., 2002)
	MK 212 (5-HT(2C/2B) receptor agonist)	1.0 mg/kg, i.p.	↓ cue ↓ cocaine	(Neisewander & Acosta, 2007)
	Ritanserin (5-HT(2) antagonist)	1.0 or 10.0 mg/kg, i.p.	↔ cocaine	(Schenk, 2000)
	Fluoxetine (selective 5-HT reuptake inhibitor)	10.0 mg/kg, i.p.	↓ cue ↔ cocaine	(Burmeister et al., 2003)
		30 mg/kg, i.p. chronic	↔ cocaine ↓ context	(Baker et al., 2001)
	d-fenfluramine (SRI/releaser)	3.0 mg/kg, i.p.	↓ cue ↔ cocaine	(Burmeister et al., 2003)
Norepinephrine	Clonidine (alpha2 agonist)	20 or 40 µg/kg, i.p.	↓ stress ↔ cocaine	(Erb et al., 2000)
	Lofexidine (alpha2 agonist)	50-200 µg/kg, i.p.	↓ stress ↔ cocaine	(Erb et al., 2000)
		0.1 or 0.2 mg/kg, i.p.	↓ stress (speedball) ↔ cue (speedball)	(Highfield et al., 2001)
	Guanabenz (alpha2 agonist/low affinity Imidazoline1 ligand)	0.64 mg/kg, i.p.	↓ stress ↔ cocaine	(Erb et al., 2000)
	Prazosin (alpha1 antagonist)	0.3 mg/kg, i.v.	↓ cocaine	(Zhang & Kosten, 2005)
	Yohimbine (alpha2 antagonist)	1.25 mg/kg, i.p. (extinction)	↔ stress (footshock)	(Kupferschmidt et al., 2009)

Table 2

Effects of non-monoaminergic classes of drugs on the reinstatement of cocaine-seeking in rats induced by cocaine, cue, stress, or context.

Class of drug	Drug	Route and dose	Effect	Reference
Glutamate (inotropic)	6-cyano-7-nitro-quinoxaline-2,3-dione (CNQX) (AMPA/kainate receptor antagonist)	3 mg/kg, i.p.	↓ cue	(Backstrom & Hyytia, 2006)
	NBQX (AMPA/kainate receptor antagonist)	5 mg/kg, i.p.	↓ cue	(Backstrom & Hyytia, 2006)
	L-701,324 (NMDA/glycine site antagonist)	1.25 or 2.5 mg/kg, i.p.	↓ cue	(Backstrom & Hyytia, 2006)
	CGP 39551 (NMDA receptor antagonist)	2.5-10 mg/kg, i.p.	↔ cue	(Backstrom & Hyytia, 2006)
	D-CPPene (competitive NMDA receptor antagonist)	3 mg/kg, i.p.	↓ cue	(Bespalov et al., 2000)
	Memantine (low-affinity NMDA receptor channel blocker)	10 mg/kg, i.p.	↔ cue	(Bespalov et al., 2000)
Glutamate (metabotropic)	2-methyl-6-(phenylethynyl)-pyridine (MPEP) (mGluR5 antagonist)	2.5 or 5 mg/kg, i.p.	↓ cue	(Backstrom & Hyytia, 2006)
	MTEP, 3-[(2-methyl-1,3-thiazol-4-yl) ethynyl]piperidine (mGluR5 antagonist)	0.3-10 mg/kg, i.p.	↓ cocaine	(Martin-Fardon et al., 2009)
	LY379268 (mGluR2/3 agonist)	1 or 3 mg/kg, i.p.	↓ cocaine	(Peters & Kalivas, 2006)
Glutamate (other)	N-acetylcysteine (activates cystine-glutamate exchange)	100 mg/kg, i.p. 60 mg/kg, s.c. 60 mg/kg, i.p. (daily in self-administration)	↓ cocaine	(Baker et al., 2003a,b) (Moran et al., 2005) (Madayag et al., 2007)
	Acamprosate	300 mg/kg, i.p.	↓ cocaine, ↓ cue	(Bowers et al., 2007)
GABA	Baclofen (GABA _B agonist)	1.25 or 2.5 mg/kg, i.p.	↓ cocaine	(Campbell et al., 1999)
		2.5-5 mg/kg, i.p.	↓ cocaine	(Filip et al., 2007b; Filip et al., 2007c)
	SCH 50911 (GABA _B receptor antagonist)	5 mg/kg, i.p. 10 mg/kg, i.p.	↓ cue ↓ cocaine ↓ cue	(Filip & Frankowska, 2007) (Filip & Frankowska, 2007)
	SKF 97541 (GABA _B agonist)	0.03-0.3 mg/kg, i.p.	↓ cocaine ↓ cue	(Filip & Frankowska, 2007)
	CGP 7930 (GABA _B allosteric positive modulator)	30 mg/kg, i.p. 10 or 30 mg/kg, i.p.	↓ cocaine ↓ cue	(Filip & Frankowska, 2007)
	Gabapentin (cyclic GABA analogue)	10-30 mg/kg, i.p. 25-200 mg/kg, i.p.	↔ cocaine	(Filip et al., 2007c) (Peng et al., 2008b)
	Tiagabine (GABA reuptake inhibitor)	10 mg/kg, i.p.	Nonsignificant ↓ cocaine	(Filip et al., 2007c)
	Vigabatrin (gamma-vinyl GABA) (irreversible inhibitor of GABA transaminase and reuptake)	150-250 mg/kg, i.p. 25-300 mg/kg, i.p.	↓ cocaine	(Filip et al., 2007c) (Peng et al., 2008a)
	Alprazolam	2 or 4 mg/kg, i.p.	↓ cue	(Goeders et al., 2009)

Class of drug	Drug	Route and dose	Effect	Reference
Opioid	Oxazepam	20 or 40 mg/kg, i.p.	↓ cue	(Goeders et al., 2009)
	JDTic (potent and selective KOR antagonist)	10 or 30 mg/kg, s.c.	↓ stress (footshock) ↔ cocaine	(Beardsley et al., 2005)
	Naltrexone	0.25-2.5 mg/kg, s.c.	↓ cue	(Burattini et al., 2008)
		1.6 or 3.2 mg/kg, s.c.	↔ cocaine	(Comer et al., 1993)
		3 mg/kg, s.c.	↓ cocaine	(Gerrits et al., 2005)
	Buprenorphine	0.025-0.4 mg/kg, i.v.	↓ cocaine	(Comer et al., 1993)
		3 mg/kg/day, minipump s.c.	↓ cocaine ↔ stress (footshock)	(Sorge et al., 2005)
	Etonitazene (opioid agonist)	2.5 or 5.0 µg/kg, i.v.	↓ cocaine	(Comer et al., 1993)
	Methadone	30 mg/kg/day, minipumps	↓ cocaine and heroin in mixed self admin ↔ stress	(Leri et al., 2004)
	nociceptin/orphanin FQ (NC) (endogenous ligand of the opioid receptor-like 1 (ORL1))	0.1-2.0 µg/kg, i.c.v.	↓ stress (footshock)	(Martin-Fardon et al., 2000)
Cannabinoid	BD1047 (potent and selective sigma1 receptor antagonist)	20 or 30 mg/kg, i.p.	↓ cocaine	(Martin-Fardon et al., 2007)
	U69593 (kappa-opioid agonist)	0.32 mg/kg, s.c.	↓ cocaine	(Schenk et al., 1999, 2000)
	Rimonabant (cannabinoid receptor CB1 antagonist/partial agonist)	10 mg/kg, i.p. 5 or 10 mg/kg, i.p.	↓ cocaine ↓ cue	(Filip et al., 2006)
	AM251 (highly selective CB1 receptor antagonist)	1-10 mg/kg, i.p.	↓ cocaine	(Xi et al., 2006a)
	WIN 55,212-2 (CB agonist)	0.3 mg/kg, i.p. 3 mg/kg, i.p.	↑ cue ↔ cue	(Gonzalez-Cuevas et al., 2007)
Hormones	Progesterone	0.5 mg/kg, s.c.	↓ cocaine in ovariectomized rat ↓ cocaine in estrous females	(Anker et al., 2007) (Anker et al., 2009) (Feltenstein et al., 2009)
	Estradiol benzoate	0.05 mg/kg, s.c.	↑ cocaine in ovariectomized rat	(Anker et al., 2007) (Larson et al., 2005)
	Dehydroepiandrosterone (DHEA)	2 mg/kg, i.p.	↓ cocaine	(Doron et al., 2006)
	Diarylpropionitrile (ERbeta-selective agonist)	1 mg/kg, i.p.	↑ cocaine	(Larson & Carroll, 2007)
	propyl-pyrazole-triol (PPT) (ERalpha-selective agonist)	1 mg/kg, i.p.	↔ cocaine	(Larson & Carroll, 2007)
	Corticosterone	50 mg pellets, p.o.	↓ stress (food deprivation) in adrenalectomized rats	(Shalev et al., 2003)
	Allopregnanolone	15 or 30 mg/kg, s.c.	↓ cocaine	(Anker et al., 2009)

Class of drug	Drug	Route and dose	Effect	Reference
Other systems	SB-334867 (selective orexin1 receptor antagonist)	30 mg/kg, i.p.	↓ stress (footshock)	(Boutrel et al., 2005)
	D-Phe CRF12-41 (CRF receptor antagonist)	0.1-1 µg/kg, i.c.v.	↓ stress (footshock)	(Erb et al., 1998)
		0.1 or 1 µg/kg, i.c.v.	↓ cocaine	
	CP-154,526 (selective, non-peptide antagonist of the CRF1 receptor)	20 mg/kg, i.p.	↓ cue	(Goeders & Clampitt, 2002)
		5-20 mg/kg, ip	↓ cocaine	(Przegalinski et al., 2005)
		15 or 30 mg/kg, s.c.	↓ stress (footshock)	(Shaham et al., 1998)
	RP 67580 (selective neurokinin 1 receptor antagonist)	0.1-2.5 nmol, i.c.v.	↔ cocaine	(Placenza et al., 2005)
	GR 82334 (selective neurokinin 1 receptor antagonist)	2-50 pmol, i.c.v.	↔ cocaine	(Placenza et al., 2005)
	Albu-CocH enzyme (human butyrylcholinesterase (BChE) fusion with human serum albumin)	2 mg/kg, i.v.	↓ cocaine	(Brimijoin et al., 2008)
	SR142948 (neurotensin antagonist)	10 µg/kg, i.p.	↓ cocaine	(Torregrossa & Kalivas, 2008)
	1-methyl-1,2,3,4-tetrahydroisoquinoline (1MeTIQ) (endogenous tetrahydroisoquinolines)	25-50 mg/kg, i.p.	↓ cocaine ↔ cue	(Filip et al., 2007a)
	Ketoconazole	25 mg/kg, i.p.	↓ cue	(Goeders & Clampitt, 2002)
		50 mg/kg, i.p.	↔ cocaine	(Mantsch & Goeders, 1999b)
		25 or 50 mg/kg, i.p.	↓ stress	(Mantsch & Goeders, 1999a)
	2E2 (anti-cocaine monoclonal antibody (mAb))	120 mg/kg, i.v.	↓ cocaine	(Norman et al., 2009)
	L-NG-nitroarginine methyl ester (L-NAME) (nitric oxide synthase inhibitor)	50 mg/kg, i.p.	↓ cocaine	(Orsini et al., 2002)

Table 3

Effect of systemic administration of different drugs on the reinstatement of methamphetamine (meth) seeking behavior in rats induced by meth or cue.

Drug	Dose and route	Effect	Reference
SR141716A (cannabinoid CB1 receptor antagonist)	3.2 mg/kg, i.p. 1 mg/kg, i.p.	↓ meth ↓ cue	(Anggadiredja et al., 2004a)
Delta8-tetrahydrocannabinol (THC) (cannabinoid agonist)	3.2 mg/kg, i.p.	↓ cue, ↓ meth	(Anggadiredja et al., 2004a)
AM251 (the CB(1) receptor antagonist)	0.032-0.32 mg/kg, i.v.	↔ meth	(Boctor et al., 2007)
Diclofenac (cyclooxygenase inhibitor)	3.2 or 10 mg/kg, i.p.	↓ cue, ↓ meth	(Anggadiredja et al., 2004a)
Naltrexone	1 mg/kg, i.p. 3.2 mg/kg, i.p.	↓ cue ↔ meth	(Anggadiredja et al., 2004b)
Ondansetron (5-HT3 receptor antagonist) plus pergolide (dopamine agonist)	0.2 mg/kg, s.c., 0.1 mg/kg, s.c. respectively	↓ meth	(Davidson et al., 2007)
MTEP (selective type 5 metabotropic glutamate receptor (mGluR5) antagonist)	1 or 3 mg/kg, i.p.	↓ cue, ↓ meth	(Gass et al., 2009)
Lobeline	1 or 3 mg/kg, i.v.	↔ meth	(Harrod et al., 2003)
Nicotine	0.1 or 0.32 mg/kg, s.c.	↓ meth, ↓ cue	(Hiranita et al., 2004)
Donepezil (acetylcholinesterase inhibitor)	0.1 or 0.32 mg/kg, i.p.	↓ meth, ↓ cue	(Hiranita et al., 2006)
Ketoconazole (adrenal steroid synthesis inhibitor)	25-100 mg/kg, i.p.	↔ meth, ↔ cue	(Moffett & Goeders, 2007)
CP-154,526 (corticotropin-releasing hormone (CRF) type 1 receptor antagonist)	20 or 40 mg/kg, i.p	↓ meth, ↔ cue	(Moffett & Goeders, 2007)

Table 4

Controlled clinical trials of potential therapeutics in cocaine and/or methamphetamine addicts.

Drug	# patients	Specific diagnoses	Result	Reference
Propranolol	108	Cocaine dependent with severe withdrawal	↑ duration of abstinence, ↓ withdrawal symptoms	(Kampman et al., 2001)
	199			(Kampman et al., 2006)
Modafinil	62	Cocaine dependent	↑ negative urine screen	(Dackis et al., 2005)
Topiramate	40	Cocaine dependent	↑ rate of abstinence	(Kampman et al., 2004)
GVG (gamma-vinyl GABA)	20	Cocaine or methamphetamine	↑ rate of abstinence	(Brodie et al., 2003)
	30	Dependent	↑ negative urine screen	(Brodie et al., 2005)
Tiagabine	45	Cocaine and opiate dependent Maintained on methadone	↑ negative urine screen	(Gonzalez et al., 2003)
	50	Cocaine and opiate dependent Maintained on methadone	↓ cocaine intake and ↑ abstinence rate	(Gonzalez et al., 2007)
Disulfiram	122	Cocaine and alcohol abusers	↑ duration of abstinence	(Carroll et al., 1998)
	121	Cocaine-dependent	↑ negative urine screen	(Carroll et al., 2004)
	20	Cocaine- and opiate dependent, Maintained on buprenorphine	↑ duration of abstinence	(George et al., 2000)
	67	Cocaine- and opiate dependent, Maintained on methadone	↓ self-reported use	(Petrakis et al., 2000)
Buprenorphine	178	Cocaine- and opiate dependent	↑ negative urine screen	(Montoya et al., 2004)
TA-CD Vaccine	18	Cocaine dependent	↑ negative urine screen	(Martell et al., 2005)
Bupropion	151	Methamphetamine dependent	↑ rate of abstinence	(Elkashef et al., 2008)
	106	Cocaine and opioid dependent maintained on methadone	↑ negative urine screen	(Poling et al., 2006)
Desipramine	160	Cocaine and opioid dependent maintained on methadone	↑ negative urine screen	(Kosten et al., 2003)
Citalopram	76	Cocaine-dependent	↑ negative urine screen	(Moeller et al., 2007)
Baclofen	70	Cocaine-dependent	↓ cocaine use in heavier users	(Shoptaw et al., 2003)
	115	Severe cocaine-dependent	↔ negative urine screen and craving	(Kahn et al., 2009)