Applying extinction research and theory to cue-exposure addiction treatments

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ABSTRACT

Aims To evaluate the efficacy of cue-exposure addiction treatment and review modern animal learning research to generate recommendations for substantially enhancing the effectiveness of this treatment.

Design Meta-analysis of cue-exposure addiction treatment outcome studies ($N = 9$), review of animal extinction research and theory, and evaluation of whether major principles from this literature are addressed adequately in cue-exposure treatments.

Findings The meta-analytical review showed that there is no consistent evidence for the efficacy of cue-exposure treatment as currently implemented. Moreover, procedures derived from the animal learning literature that should maximize the potential of extinction training are rarely used in cue-exposure treatments.

Conclusions Given what is known from animal extinction theory and research about extinguishing learned behavior, it is not surprising that cue-exposure treatments so often fail. This paper reviews current animal research regarding the most salient threats to the development and maintenance of extinction, and suggests several major procedures for increasing the efficacy of cue-exposure addiction treatment.

KEYWORDS Addiction therapy, conditioning, cue-exposure treatment, extinction, meta-analysis.

INTRODUCTION

Cue-exposure has been advocated as a potentially effective means of treating addictive behaviors (Heather & Bradley 1990; Hammersley 1992). It is widely recognized, both clinically and empirically, that drug use and relapse are often strongly cue- and context-specific (e.g. Drummond *et al.* 1995). When an addict encounters cues previously paired with drug-use, for example drug paraphernalia or contexts in which drugs were taken, they evoke responses such as drug-seeking behavior and withdrawal-like symptoms that are presumed to motivate or mediate drug use. This observation led researchers to consider the therapeutic benefit of diminishing the associative impact of drug cues using procedures derived from basic animal extinction research.

Typically, cue-exposure treatment involves repeated unreinforced exposure to stimuli associated previously with drug use in an attempt to extinguish an addict's conditioned responses to such cues. This technique has been utilized in treatments across most drugs of abuse including opiates (e.g. Ehrman *et al.* 1998), alcohol (e.g. Drummond & Glautier 1994) and nicotine (e.g. Raw & Russell 1980). The clinical success of these treatments has been less than promising, leading some researchers to investigate whether cue-exposure proves more effective when used in combination with cognitive-behavioral techniques such as social skills training (Cooney *et al.* 1983), cue replace-

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ment (Symes & Nicki 1997) or coping strategies (Monti *et al.* 1993).

The task of identifying effective supplements to cue-exposure therapy may be premature. Although this approach might, through serendipity, enhance the efficacy of treatment, attempts to improve cue exposure might be more productively informed by a return to the basic premise of this treatment. That is, systematic decisions for improving cue-exposure treatment can be guided by principles derived from animal extinction research. We acknowledge that there are limitations in translating such findings into procedures for improving cue-exposure treatment for humans. However, basic animal learning models are the basis on which cue-exposure addiction treatment was originally built; and yet, while animal learning research has advanced considerably, an evaluation of current cue-exposure treatments reveals that they fail to incorporate what is now known about extinguishing learned behavior. Until new findings from basic research and contemporary theories of conditioning are incorporated into the task of improving treatment techniques, cue-exposure's full potential for treating addictive behaviors, either alone or in combination with other psychotherapies, will not be realized.

The purpose of this paper is to (1) review the methods utilized in cue-exposure addiction treatment studies; (2) offer a meta-analysis of cue-exposure's effectiveness as a treatment for addiction; (3) review specific threats to extinction as derived from animal extinction research; and (4) suggest specific means of translating findings from animal work into viable techniques for improving cue-exposure treatment.

THE BASIS OF CUE-EXPOSURE TREATMENT

The rationale for using cue-exposure to treat addictive behaviors is based most commonly on a classical conditioning model of learning. From this perspective, the drug is the unconditioned stimulus (US) and the drug effects are the unconditioned responses (UR). The conditions under which the drug is used become conditioned stimuli (CS) that evoke conditioned responses (CR) that moderate or mediate drug seeking and drug consumption. Generally, these CRs have been conceptualized in terms of positive-incentive processes (e.g. Stewart, de Wit & Eikelboom 1984) and/or withdrawal-like symptoms (e.g. Wikler 1948; Siegel 1983). For example, consider an individual who smokes a cigarette and experiences the direct effects of nicotine, including increases in heart rate and sweat gland activity and decreases in body temperature (Goodman & Gilman 1996). The smoker might also experience subjective effects such as changes in mood or mental state. As the smoker continues to use cigarettes, the situations in which smoking occurs are repeatedly paired with the drug itself and acquire the properties of CSs. Over time, these situations alone evoke CRs that may generate craving and motivate drug-seeking behavior.

The assumption that addicts display significant subjective and physiological reactions to stimuli associated with drug use is supported empirically by both animal and human research. The earliest evidence of drug conditioning in animal research comes from the work of Pavlov (1927), who demonstrated that animals could display learned responses to contextual stimuli associated previously with the onset of drug effects (Pavlov 1927). Since that time, conditioned responses produced by drug administration have been reported in animal research across a variety of drugs of abuse (Glautier & Remington 1995).

Human research also offers considerable evidence that addicts confronted with cues associated with past drug use exhibit increases in craving and autonomic activity (Niaura *et al.* 1988; Rohsenow *et al.* 1990; Robbins & Ehrman 1992; Carter & Tiffany 1999). Some research has also demonstrated extinction of responses to drug-related stimuli. For example, O'Brien *et al.* (1990) found that cocaine addicts exhibited significant decreases in subjective and physiological reactivity to cocaine-related stimuli following systematic non-reinforced exposure to drug cues. In addition, this research has shown that autonomic responses exhibit weaker levels of extinction in comparison to addicts' self-report (O'Brien *et al.* 1990).

The methods by which researchers have translated these findings into treatments for addictive behaviors have varied only slightly across drugs of abuse. Typically, addicts are exposed to personally relevant drug cues, either *in vivo* (i.e. handling drug paraphernalia) or imaginal (i.e. imagining being in a situation typical of past drug use), in the absence of drug ingestion. The goal of these techniques is to extinguish learned responses to drug cues through repeated nonreinforced exposure.

REVIEW OF METHODS FOR CONDUCTING CUE-EXPOSURE ADDICTION TREATMENT

To date, results from 18 non-case study cue-exposure treatment studies for addiction have been published. Several studies involved procedures not identified specifically as 'cue exposure' (e.g. response prevention, cue extinction); however, any treatment involving exposing addicts to cues associated with past drug use in an attempt to extinguish learned responding to those cues

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was included in this review. On the other hand, some studies involved exposure to drug cues for the purpose of replacing a learned response with an alternative response (e.g. covert sensitization). These studies were not included in this review. A summary of the 18 studies' treatment components is presented in Table 1. These studies comprise a generally homogeneous group, as techniques vary only slightly between them and common methodological trends are apparent.

Referring to Table 1, cue exposure treatment studies have been conducted with individuals addicted to opiates ($N = 6$), nicotine ($N = 5$), alcohol ($N = 5$) and cocaine ($N = 1$). One study (Childress *et al*. 1987) included both opiate and cocaine addicts. It was equally common for treatment to be conducted in inpatient and outpatient settings across studies; however, treatment for nicotine addiction was always provided on an outpatient basis and cocaine treatment was always performed in an inpatient setting. Individual therapy was more prevalent than group therapy, with only four studies conducting cue-exposure sessions within groups. Group therapy was limited to nicotine- and alcohol-treatment studies.

Approximately half of the studies were conducted with participants who were drug-free during treatment ($N = 9$). Of the remaining studies, variations in abstinence status occurred for a variety of reasons. In one study with opiate addicts participants were given daily doses of naltrexone, an opiate antagonist, and received hydromorphone during treatment (O'Brien *et al*. 1979). In another, participants were maintained on methadone (McLellan *et al.* 1986). In one alcohol study, non-dependent alcohol abusers with a modified drinking goal were given priming doses and told to refrain from further drinking; in addition, they practiced the same procedure outside of the treatment session for homework (Sitharthan *et al.* 1997). Similarly, priming doses of alcohol paired with response prevention were utilized in a study with alcoholic inpatients (Rankin *et al.* 1983). Participants in nicotine studies were the least likely to be abstinent during treatment. In one study, cue-exposure treatment was combined with nicotine replacement therapy (i.e. nicotine gum). In two others, participants were not instructed to quit until half of the cue-exposure sessions had been conducted (Lowe *et al.* 1980; Götestam & Melin 1983). Finally, researchers in a fourth study never specifically instructed smokers to quit and several of the participants continued smoking throughout treatment (Corty & McFall 1984).

Cues have been presented through various modes during cue-exposure addiction treatment, including photographic, video, audio, imaginal and *in vivo* presentations of cues. Photographic cues included pictures and slides of drug paraphernalia and addicts in various stages of drug use. Video cues included scenes in which an individual engaged in drug use or drug purchase. Audio cues were recordings of individuals using drugs or talking about drug-use behavior (e.g. making a drug purchase, describing drug sensations). Imaginal cues required active imagination of self-produced verbal imagery of drug use routine (i.e. 'drug story'), personal drug use 'triggers', and standardized scenarios likely to evoke drug urges (e.g. a stressful day at work, drinking coffee). *In vivo* cues included handling one's own or simulated drug paraphernalia and drug itself, ingestion of actual drug (e.g. priming doses of alcohol) or simulated drug (e.g. injecting saline), preparing drugs for use (e.g. lighting a cigarette, 'cooking up' and 'tying off'), and outside exposure in an environment associated with past drug use. Only one study incorporated all modes of cue presentation (McLellan *et al*. 1986). Eight studies utilized only one mode and nine included two or more. The most prevalent mode of presentation was *in vivo*, with 15 of the 18 studies including at least one *in vivo* cue.

The number of cue-exposure sessions varied greatly across studies, with a range of 2–35 sessions. The length of treatment sessions ranged from approximately 40 to 90 minutes, with the actual amount of cue-exposure time ranging from approximately 10–60 minutes per session. The number of cues presented during any single cue-exposure session varied from one to nine. One of three methods was used for determining how long a participant was exposed to any one cue: (1) a specific amount of time was predetermined (e.g. smelling a glass of alcohol for three minutes; Drummond & Glautier 1994); (2) a specific action was required and when it was completed exposure to that cue ended (e.g. preparing a heroin syringe; O'Brien *et al*. 1979); and (3) the exposure was terminated when the participant's self-reported craving/urge level dropped to half the peak intensity experienced during exposure to the target cue (Monti *et al*. 1993). Treatment sessions either occurred for a set number of days, for example, 10 consecutive days (massed; e.g. Childress *et al*. 1987), or were distributed across a specific number of days, for example, five sessions over 14 days (spaced; e.g. Niara *et al*. 1999).

EFFECTIVENESS OF CUE-EXPOSURE TREATMENT FOR ADDICTION

The effectiveness of cue-exposure treatment was evaluated by applying meta-analytical techniques to the abstinence or drug-use reduction results from each treatment outcome study. Of the 18 cue-exposure studies reviewed here, only 12 included a follow-up procedure for measuring abstinence or reduction in drug use. Of those 12, three studies revealed very little about the efficacy of cue-exposure treatment, as one study contained no control or

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Table 1 Summary of cue-exposure treatment studies.

Study	Drug[a]	I/O[b]	I/G[c]	Adjunct treatment[d]	Abstinent[e]	No. of sessions[f]	CE length (min.)[g]	Session spacing[h]	Exposures per session[i]	Cues[j]	Criteria for ending exposure[k]	Follow-up[L]	Effect size (d =)[m]
Corty & McFall (1984)	N	OP	I	Y	N	8	NI	M	1	A	F	1, 3, 6 months	–0.4500
Childress ***et al.*** (1987)	O/C	IP	G	Y	Y	20	60	S	9	A,V,IV	F	—	—
Dawe ***et al.*** (1993)	O	IP	I	Y	Y	6	41–80	S	2	P,V,IV	R-B	6 weeks, 6 months	+0.0805
Drummond & Glautier (1994)	A	IP	I	N	Y	10	50	M	2	IV	F	1, 3, 6 months	+0.17–3
Franken ***et al.*** (1999)	O	OP	I	N	Y	9	45–50	S	V	P,V,IV	R-B	6 weeks	—
Götestam & Melin 1983)	N	OP	I	N	Y/N	6	NI	M	1	I	F	1 month	—
Kasvikis ***et al.*** (1991)	O	IP	I	N	Y	14	45	M	V	P,IV	R-B	1, 3, 6 months	—
Lowe ***et al.*** (1980)	N	OP	G	Y	Y/N	8	V	S	1	IV	R-B	48 h, 3, 6 months	–0.5180
McLellan ***et al.*** (1986)	O	OP	I	Y	Y[1]	35	10–15	S	V	P,A,V,I,IV	F	—	—
Monti ***et al.*** (1993)	A	IP	I	Y	Y	6	55	S	3	I,IV	R-B	0–3, 3–6 months	+0.7345
Niaura ***et al.*** (1999)	N	OP	I	Y	N[2]	5	75–90	S	4	I,IV	R-B	1, 3, 6, 12 months	–0.2029
O'Brien ***et al.*** (1990)	C	IP	I	Y	Y	15	60	S	3	A,V,IV	F	—	—
O'Brien ***et al.*** (1979)	O	OP	I	Y	Y[3]	18	60	S/M	1	IV	F	6 months	—
Powell ***et al.*** (1993)	O	IP	I	Y	Y	2	45–50	S	V	P,IV	R-B	—	—
Rankin ***et al.*** (1983)	A	IP	I	Y	N[4]	12	65	S	1	I,IV	F	—	—
Raw & Russell (1980)	N	OP	G	Y	Y/N	7	45	S	V	IV	F	3, 6, 12 months	–0.0251
Rohsenow ***et al.*** (2000)	A	IP	I	Y	Y	10	50	M	V	I,IV	R-B	6, 12 months	+0.5420
Sitharthan ***et al.*** (1997)	A	OP	G	Y	N	6	90	S	2	IV	F	6 months	+0.6070

[a] Drug of abuse: A = alcohol; N = nicotine; C = cocaine; O = opiate [b] Treatment setting: IP = inpatient; OP = outpatient [c] Therapy: I = individual; G = group. [d] Adjunct treatment used with cue exposure? Y = yes; N = no. [e] Abstinence status: Y = abstinent; N = non-abstinent; Y/N = smoking cessation study in which abstinence started halfway through treatment or smokers were not specifically told to quit
[1] Patients maintained on methadone' [2] some patients maintained on nicotine replacement; [3] some patients maintained on naltrexone; [4] patients instructed to control drinking (2–3 drinks per occasion), but remain abstinent on treatment days. [f] Number of cue-exposure treatment sessions. [g] Minutes of cue-exposure per session: NI = no information given; V = variable. [h] Spacing of treatment session: M = massed (daily sessions); S = spaced (other than daily sessions). [i] Number of cue exposures per treatment session: V = variable [j] Cues: A = audio; P = photographic; V = video; I = imagery; IV = ***in vivo***. [k] Criteria for ending exposure: F = fixed; R-B = response-based [L] Follow-up: Dash = no follow-up conducted [m] Effect size: Dash = information allowing for the calculation of an effect size not given.

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comparison treatment group (Kasvikis *et al.* 1991), another included only a narrative description of treatment effectiveness (O'Brien *et al*. 1990) and a third reported only a rank ordering of treatment groups based on outcome (O'Brien *et al.* 1979).

The remaining nine studies met the following two criteria and were included in the meta-analysis: (1) the study included a control or comparison treatment group and (2) a post-treatment follow-up, during which abstinence or drug use was measured, was reported for each group. [Two raters, using a coding manual developed for this study, selected statistics independently from each of the nine studies included in the meta-analysis. The raters agreed on seven of nine cases. Discrepancies were resolved by discussion.] Effect sizes for each of the nine studies meeting these criteria appear in Table 1. Effect sizes, computed with the aid of DSTAT, a computer program for meta-analytical reviews of research literature (Johnson 1989), were indexed as *g*. This coefficient represents the difference between abstinence or level of drug use for the cue-exposure and comparison treatment groups divided by a pooled standard deviation (Hedges & Olkin 1985). Effect sizes showing greater abstinence or less drug use for the cue-exposure treatment group were assigned a positive value, while negative values denoted less abstinence or greater drug use for the cue-exposure group.

The *g*s were converted to *d*s by correcting them for bias (i.e. overestimates of the population effect size as a result of small sample size). This procedure gives more weight to effect sizes that are estimated more reliably. The individual effect sizes were combined to obtain the average *d*, an estimate of the overall effect size. To determine whether effect sizes were consistent across studies, they were tested for homogeneity using the *Q* statistic, which has an approximate χ^2 distribution with *k*-1 degrees of freedom, where *k* is the number of effect sizes (Hedges & Olkin 1985). The overall effect size for cue-exposure treatment (d = 0.0868; 95% confidence interval -0.11 ± 0.28) was not significant. The *Q* statistic reached significance ($Q(9) = 16.078$; $p = 0.0413$), indicating that effect sizes were not consistent across studies. In light of the relatively small number of studies contributing to the meta-analysis, it was not possible to conduct a statistically meaningful evaluation of the sources of heterogeneity across studies.

IMPROVING CUE-EXPOSURE TREATMENT

The finding that cue-exposure failed to prove efficacious in treating addiction will probably come as no surprise to most addiction researchers. Several researchers speak of the promise of cue-exposure treatment and advocate its inclusion in drug treatment studies (e.g. Heather & Bradley 1990; Hammersley 1992). Nevertheless, those providing cue-exposure treatment conclude almost invariably that there is little evidence for its effectiveness in preventing relapse among drug-dependent patients (e.g. Dawe *et al.* 1993; Powell *et al*. 1993; Franken *et al.* 1999). However, many researchers contend that cue-exposure has potential merit, and there is a pervasive belief that if the optimal parameters for cue-exposure could be discovered (e.g. the right cues are chosen, the best number of sessions are conducted, it is combined with the right psychotherapy) addiction treatment might have a new 'gold standard' for treatment efficacy.

Rather than simply trying new things in an effort to discover the optimal parameters for use in cue-exposure addiction treatment, ideas for improving treatment techniques can be directly informed by recent animal learning research focusing on extinguishing learned behavior. In fact, consideration of contemporary learning research reveals that ideas about extinction have changed considerably since cue exposure was first introduced as a treatment for addiction. For many years, extinction training was believed to lead to a weakening of the initially conditioned CS–US association (e.g. Mackintosh 1974; Rescorla & Wagner 1972). However, current concepts about extinction resemble more closely the original ideas of Pavlov (1927), who postulated that repeated unreinforced exposure to the CS does not break original CS–US learning, but rather serves to mask it (Robbins 1990). Therefore, the conventional notion that extinction is unlearning has been replaced with the position that extinction is new learning, that is, during extinction, CS–US learning remains intact, but new associations develop to the original CS. From this perspective, the effectiveness of extinction, and similarly the efficacy of cue exposure, is determined by the probability that exposure to an extinguished drug cue post-treatment will evoke behavior learned during extinction (i.e. abstinence) rather than that learned during original conditioning (i.e. drug use).

In addition to these conceptual changes with regard to understanding extinction, basic animal research has identified several factors or processes that can threaten the development and maintenance of extinction training. The most prominent of these include: the renewal effect, spontaneous recovery, reinstatement and failure to extinguish the most salient conditioned cues. Each of these phenomenon will be explained and conceptualized with regard to cue-exposure treatment. The goal of the following sections is to translate what is known from animal extinction work into specific techniques for improving cue-exposure treatments for addiction. These sections will also identify key questions that have not been addressed systematically by animal research, questions of

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potential immediate relevance to the development of more effective cue-exposure treatments.

THREATS TO EXTINCTION

Renewal effect

Animal learning research has demonstrated that the contexts in which conditioning and extinction occur play a major role in determining how an animal will respond when re-exposed to extinguished cues (e.g. Bouton & Bolles 1979; Grahame *et al.* 1990). It may be difficult to maintain a clear distinction between contexts and cues, as a context can play a variety of roles, including that of a CS. However, in the present paper, contexts will be conceptualized as situations in which drug use takes place, situations within which more proximal cues are paired with drug taking and become conditioned stimuli (CSs). Contexts alone may not evoke conditioned responses, but they may be necessary for the expression of learned responding. That is, the context can set the stage for the type of responding (i.e. original conditioning or extinction) that will be exhibited by the animal (Bouton 1993).

One clear demonstration of the role of contexts in extinction is that a switch in contexts following extinction can lead to the emergence of the original conditioned response. This effect is referred to as *renewal* and can be conceptualized as follows: when a conditioned stimulus (CS) is paired with an unconditioned stimulus (US) in one context, that is, context A (conditioning context), and is then extinguished in a different context, context B (extinction context), a return to context A (or even a new context) will renew responding to the target stimulus (Bouton 1994). This effect is readily applicable to cue-exposure treatment. Consider a heroin addict who shoots up at home (context A), then receives cue-exposure treatment in a hospital room (context B). Following treatment, the addict returns home (context A) and relapses.

One way in which the renewal effect has been conceptualized is that, following extinction, the CS has acquired two meanings: one associated with the original conditioning and one associated with extinction. The context in which the cue is presented determines which of those two meanings will be expressed. Using the previous example, in context A (home), the sight of drug paraphernalia signals use, in context B (hospital), the same stimuli signal abstinence. According to this conceptualization, renewal will be attenuated if CS responding is extinguished in the context in which the original CS–US pairing occurred. There are only two cue-exposure studies in which researchers attempted to treat addicts in their original conditioning environments by taking them to locations associated with prior drug use (e.g. a corner where drugs were bought, having them talk to a dealer or current addict) (Dawe *et al.* 1993; Kasvikis 1991). Indeed, animal research provides evidence that extinguishing cues in the original conditioning context decreases renewal (Bouton 1994). Unfortunately, renewal may be attenuated only in that context. Bouton & Ricker (1994) found that when extinction occurred in the original conditioning context, responding to the CS was eliminated, but subsequent testing of the CS in a new environment led to renewal of conditioned responding. Apparently, whereas conditioning generalizes readily, extinction is largely context dependent (Bouton 1994).

Fortunately, recreating or returning to the original conditioning context is not the only or even the most effective means of attenuating renewal. Recent animal research suggests that extinguishing cues in multiple contexts decreases the context specificity of extinction (Gunther *et al.* 1998; Chelonis *et al.* 1999). When animals received extinction training in several novel contexts and were later tested in the original conditioning context, they exhibited responding indicative of extinction. It appears that extinguishing responding in multiple domains increases the generalizability of extinction.

There are several unanswered questions about the use of multiple extinction contexts in cue-exposure treatments. First, how many different contexts are required to increase the generalizability of extinction? One animal study has shown that renewal is attenuated only if the number of extinction environments exceeds the number of conditioning contexts (Chelonis *et al.* 1999). Given the large number of possible contexts in which an addict may use drugs, it may be almost impossible to either identify or achieve the number of contexts required for complete generalization of extinction. However, perhaps there is an absolute value at which maximum extinction generalizability occurs, or it may be the case that the number of contexts needed differs considerably across drugs of abuse. For example, a smoker has probably paired numerous environmental cues with drug use, whereas a heroin addict may not have. Only future research can determine the range of contexts needed to decrease the possibility of renewal.

Secondly, there are numerous ways to make extinction contexts different, but which alterations are meaningful? In animal studies, contexts are made distinctive by varying numerous sensory aspects of the environment (e.g. the lighting, smell, size or feel of the surroundings). Thus far, no research has identified which changes are likely to be most important. If capturing attributes likely to be associated with original conditioning contexts is of primary importance, contexts should be altered with regard to an individual's past experiences with drug use.

Thirdly, the ease with which numerous contexts can be created or used will certainly vary as a function of

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treatment setting. On inpatient units, treatment sessions might be restricted to the indoors or to specific rooms. In addition, providing exposure in a naturalistic setting may be more difficult with different types of addicts. Certainly, returning a heroin addict to the streets could be potentially dangerous. In such cases, simulated natural settings may serve as useful, and safe, alternative contexts. Incorporating multiple contexts into treatment may also complicate the assessment of dependent variables; however, there should be little difficulty collecting self-report measures across a variety of settings. Further, telemetric assessment of physiological reactions via hand-held microcomputers would allow for mobile recording across a range of contexts (see Dickerson *et al.* 1988).

Bouton (1993) suggested an additional explanation for the renewal effect that has implications for cue-exposure treatment. He proposed that renewal may be due to a failure to retrieve a memory of extinction. Upon returning to the conditioning context, the subject recalls a memory of conditioning, not extinction, and reacts accordingly (e.g. uses drugs). One method of enhancing a memory of extinction that has been studied in the animal literature is to condition an extinction reminder. Bouton & Brooks (1993) found that when a novel cue was paired with extinction and presented during a return to the original conditioning context renewal decreased; that is, the subject responded as if in the extinction context. Therefore, a specific cue paired explicitly with extinction appears to increase extinction generalizability.

The use of an extinction reminder could be incorporated readily into drug cue-exposure treatment. In fact, researchers in the animal extinction field (Chelonis *et al.* 1999; Bouton 2000) have made this suggestion. However, no cue-exposure addiction treatment to date has utilized this technique. Several guidelines for implementing this technique seem evident. First, the extinction cue should be compact, allowing for easy mobility and access. Secondly, it should be novel, so it elicits only a memory of extinction. Thirdly, over the course of treatment it should be presented to the addict only during extinction training. Fourthly, following treatment, it should be used only when the addict needs a reminder of extinction so as to avoid degradation of its effectiveness due to familiarity. Finally, the addict should be trained to deploy the cue in immediate anticipation of a high-risk situation.

Spontaneous recovery

Animal research demonstrates that extinguished responses can re-emerge when the CS is presented at some time after the extinction training sessions (e.g. Brooks & Bouton 1993; Pavlov 1927; Robbins 1990; Rescorla 1997). In contrast to the renewal effect, which is contingent upon contextual changes, spontaneous recovery occurs following the passage of time from extinction to re-exposure to the CS. Therefore, attenuating spontaneous recovery requires consideration of the temporal spacing of cue-exposures. This includes within-session spacing, referring to the frequency of exposure to a cue and the amount of time between cue exposures, as well as between-session spacing, referring to the amount of time from one exposure session to the next.

With regard to within-session frequency, Berman & Katzev (1972) found that the rate of extinction learning was significantly faster when rats were given a series of short exposures to the CS versus a single massed presentation. This is notably different than the procedures typically used in cue-exposure treatments. Many of the treatment studies reviewed provided multiple short cue exposures in one session, with each exposure involving a new cue. This method prevents any one cue from becoming fully extinguished, as the full extinction of a cue requires multiple presentations of that cue within one session. Of the studies that used only one cue, cue exposures were often long and, in some studies, occurred only once per session. No animal research has shown that one unreinforced exposure is adequate to extinguish a conditioned cue.

In addition, animal work reveals that longer intertrial intervals (ITIs) between exposure to the same cue leads to sustained extinction (Mackintosh 1974). That is, allowing time between exposures to one cue allows for recovery of responding to that cue within session, at which time additional extinction training can be conducted. Although this slows the rate of extinction, it allows for cues to be extinguished more completely, with a corresponding decline in vulnerability to spontaneous recovery post-treatment.

Between-session spacing is also an important moderator of spontaneous recovery. Rescorla (1997) found that responding to extinguished cues returned in one group of rats tested 8 days post-extinction compared to another group tested immediately following extinction. Review of addiction cue-exposure methods reveals that treatment sessions are conducted primarily for several consecutive sessions or across a short period of time, after which treatment ceases. Animal studies have shown that spontaneous recovery appears inevitable if extinction trials are distributed in relatively isolated temporal or spatial pockets (Bouton 1993). When blocks of extinction sessions are spread out, spontaneous recovery is attenuated. Moreover, research has shown that the magnitude of spontaneous recovery declines over the course of additional extinction trials. Therefore, cue-exposure sessions should be spaced to allow for maximal re-emergence of responding at which time extinction can be conducted

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again. Robbins (1990) found that, following extinction to an appetitive stimulus, spontaneous recovery in rats was maximal at 48 hours. It would be beneficial to know the time interval within which spontaneous recovery peaks in human subjects, so that cue-exposure sessions could be spaced to allow for maximal spontaneous recovery prior to additional extinction.

Several guidelines for structuring cue-exposure treatment sessions can be derived from animal extinction research. First, within a given session, a cue should be presented several times to ensure complete extinction. In order to determine that a cue has been extinguished, measures of reactivity must be tracked during the session. Within-session exposures to the same stimulus should be separated by a sufficient amount of time to permit some recovery of responding between exposures. It may be more efficient to extinguish two stimuli in one session, alternating between the two so that recovery to each can occur followed by additional unreinforced exposure. Spacing between sessions should be long enough to allow for spontaneous recovery and further extinction. If different cues are used in subsequent sessions, consecutive days could be utilized. Extinguished cues should be represented in later exposure sessions to enable further extinction following the passage of time; however, ample time should elapse prior to re-exposure to such cues. The number of extinction sessions required for effective cue-exposure treatment should be determined by each patient's individual pattern of responding. That is, extinction should continue until CSs no longer evoke reactions following the passage of time.

In order to make systematic decisions regarding the spacing of cue exposures and treatment sessions, future research must determine the best method of tracking extinction learning. Cue-reactivity research has shown that no one measure of responding, subjective, physiological or behavioral, captures uniquely addicts' full responsivity to evocative drug stimuli (Tiffany 1990; Tiffany & Conklin 2000). The value of each of these response measurements as an indicator of extinction learning is unknown. Moreover, research has yet to determine which indices of responding are predictive of sustained extinction to drug cues post-treatment. Until future research defines the underlying mechanisms and function of various modes of reactivity, cue-exposure treatment should incorporate methods of measuring responding across more than one domain [see Cacioppo & Tassinary (1990).

Reinstatement

Reinstatement is a phenomenon whereby responding to an extinguished CS re-emerges as a consequence of post-extinction exposures to a US. Like renewal, reinstatement is strongly influenced by contextual componenets (e.g. Bouton 1994). After a CS has been extinguished, responding can be reinstated by presenting the US alone in the conditioning context. When the extinguished CS is subsequently presented alone in that context, conditioned responding can occur as it did prior to extinction. This phenomenon can be observed in instrumental paradigms as well where priming doses of drug have been shown to reinstate extinguished responding (Carroll & Comer 1996; de Wit 1996). For example, de Wit & Stewart (1981) trained rats to lever-press for cocaine and then extinguished lever-press responses. Following extinction, delivery of non-contingent cocaine doses in the training context reinstated lever-pressing.

Although it may not be common for addicts to experience non-contingent re-exposure to illegal drugs, it is common for addicts in recovery to be exposed to drugs such as painkillers or cough medicines that may contain narcotics or alcohol. In addition, it is common for addicts to experience a lapse in abstinence. Such re-exposure to drugs can quickly reinstate learned responding to extinguished drug cues. Reinstatement poses a strong threat to the effectiveness of cue-exposure addiction treatments. In theory, once an addict relapses in a context where CS–US pairing occurred, all extinguished cues may once again evoke the original conditioned responding. Evidence from animal research has shown that reinstatement is attenuated by reducing context conditioning. That is, giving the subject lengthy exposure to the context alone, following re-exposure to US in that context, reduces reinstatement (e.g. Bouton 1994; Bouton & Bolles 1979). Therefore, if an abstinent addict has a lapse but is able to avoid continued use, further unreinforced exposure to the context in which the US re-occurred should reduce the threat of extinguished cues being reinstated in that environment.

Some researchers have suggested that non-specific aspects of cue-exposure treatment may actually attenuate reinstatement. That is, during treatment sessions, patients may be gaining increased confidence in their ability to abstain from drug use in the face of salient cues, or they may be developing coping strategies for dealing with lapses in abstinence (Drummond & Glautier 1994). If addicts are able to keep from returning to regular drug use following a lapse, the benefits of cue-exposure should remain intact (Bouton 1994). Several of the treatment outcomes studies reviewed here found that initial lapses following cue-exposure treatment did not lead to immediate re-addiction (e.g. Monti *et al.* 1993; Drummond & Glautier 1994). As noted earlier, many researchers have tried combining cue-exposure with various psychotherapy techniques in an attempt to increase treatment efficacy (e.g. Cooney *et al.* 1983). The animal extinction work suggests that psychotherapy aimed at preparing

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addicts to cope effectively with lapses and maintain further abstinence may be the most useful supplement to cue-exposure treatment.

Types of cues extinguished

There is an implicit assumption within the cue-exposure paradigm that conditioned responses serve as mediators between drug cues and drug use. That is, reactivity to drug cues directly brings about drug-use behavior. Animal experiments have demonstrated that conditioned responding to drug cues can be extinguished through repeated presentation of the CS without the US (Siegel 1979; Mansfield & Cunningham 1980; Siegel *et al.* 1980; Cepeda-Benito & Tiffany 1995). If, indeed, CRs are the causal pathway between cue exposure and drug use, then an extinction-based treatment should prove powerful in eliminating drug use. However, drug use may involve instrumental as well as classical conditioning. That is, drug cues may operate not only as CSs but may also serve as discriminant stimuli (S^Ds) for drug administration. For example, a bottle of an alcoholic's favorite beverage (CS) may elicit conditioned responses by virtue of its frequent pairing with alcohol effects. At the same time, the bottle may serve as an S^D that sets the occasion for drinking behavior, which is reinforced positively by the effects of alcohol. Thus, even if conditioned responses to the bottle cues are extinguished, the instrumental act of drinking will remain intact. Without extinction of those behaviors, it is unlikely that extinction of classically conditioned responses in this scenario will be sufficient to eliminate drug use.

In an instrumental paradigm, if a rat presses a lever to self-administer drug, lever-pressing leads to the positive outcome of drug effects. Certainly, other stimuli in the chamber may also gain associative properties, that is become CSs (e.g. a light, a scent). If, during extinction, the lever is removed, thereby disallowing the action of drug taking, lever-pressing will not be extinguished. Even if all evocative CSs in the chamber are extinguished, so that the rat no longer associates the chamber with drug use, as soon as the lever is reintroduced the rat will once again lever-press to administer drug. In order to stop drug administration, the lever must remain in the chamber and the rat be permitted to lever-press without subsequent drug reinforcement.

Cue-exposure addiction treatment, as it is currently conducted, is analogous to taking the lever out of the rat's chamber and focusing extinction on the CSs (e.g. the light, the scent) that have been reliably paired with the drug (Tiffany 1995). With the exception of one study (O'Brien *et al.* 1979), none of the cue-exposure treatments reviewed here exposed addicts to unreinforced drug administration in an attempt to extinguish drug taking behavior. Some studies have exposed addicts to drug-use preparation but have stopped short of actual administration. For example, Raw & Russell (1980) had smokers light cigarettes and sometimes take non-inhaled puffs. Dawe *et al.* (1993) had addicts prepare for heroin use in a simulated cook-up procedure. Although these methods involved exposure to elements of the drug routine, they did not allow for extinction of actual drug administration.

One means of exposing addicts to unreinforced drug administration is through the use of drug antagonists that block or counteract drug effects pharmacologically. For instance, naltrexone, an opiate-antagonist, blocks the euphoric effects of heroin, morphine and other opiate derivatives (e.g. Platt *et al.* 1999). Similarly, mecamylamine, a nicotine antagonist, has been utilized in smoking cessation (Rose *et al.* 1998). These antagonists can be administered prior to drug ingestion, resulting in unreinforced drug use. However, treatments incorporating drug antagonists may have a crucial drawback. Research has demonstrated that the pharmacological effects of naltrexone and mecamylamine can be distinguished from saline in a drug discrimination task (e.g. France & Woods 1985; France & Woods 1987). If the pharmacological effects of drug antagonists are discernable, they may produce interoceptive cues that, once eliminated post-treatment, would leave the addict in a state more similar to that experienced during conditioning than that of extinction. Consequently, following treatment, in the absence of the interoceptive cues provided by the antagonist, the addict would be likely to experience a renewal of conditioned responding when confronted with drug stimuli.

An alternative to using drug antagonists as a means of exposing addicts to unreinforced drug administration is to have addicts self-administer placebo. For example, therapists can have heroin addicts cook-up and inject saline, smokers inhale de-nicotized cigarettes or alcoholics drink non-alcoholic beer. Some researchers have noted that these techniques can cause addicts considerable frustration that may lead to low treatment compliance (O'Brien *et al.* 1979). In the only published cue-exposure study examining this approach, O'Brien *et al.* (1979) had heroin addicts either inject saline or inject heroin while maintained on naltrexone. The authors reported that participants experienced substantial frustration and refused to continue treatment following a few initial exposures (O'Brien *et al.* 1979).

It is difficult to draw any conclusions from the O'Brien *et al.* (1979) study, as no measure of frustration was utilized and only a small sample of addicts participated. Nonetheless, it is not surprising that unreinforced drug administration might lead to considerable frustration. Drug ingestion is highly rewarding. If an addict is not

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reinforced for a routine that has previously, and almost invariably, led to desired drug effects, frustration seems a likely result. Theories of frustration in the animal extinction literature state that the amount of frustration produced by unreinforced exposure is a direct function of the level of expectation of reinforcement and/or incentive motivation, both of which are presumably high in drug administration. Moreover, the strength of extinction is proposed to be a direct function of that level of frustration (Mackintosh 1974).

Further investigation of the effectiveness of unreinforced drug administration as a component of cue-exposure treatment is needed. Primary research should focus on understanding and possibly reducing the discomfort associated with this procedure. It is probable, however, that this technique will produce discomfort, regardless of attempts to decrease its aversiveness. Therefore, a more productive step might be to establish a sound treatment rationale and prepare addicts systematically for the discomfort this component of treatment will probably entail.

THE FUTURE OF CUE-EXPOSURE TREATMENT

In spite of considerable advocacy for cue-exposure's potential effectiveness in treating drug addiction, the meta-analysis conducted here reveals that current methods fail repeatedly to increase abstinence among drug-dependent patients. Moreover, attempts to increase cue-exposure's treatment efficacy have been largely unsystematic and have not promoted the development of more successful treatment techniques. However, cue-exposure's lack of efficacy is not surprising considering what animal extinction research and theory reveal about extinguishing learned behavior.

Certainly, differences between animal and human addicts create limitations in directly translating findings from animal laboratories into cue-exposure treatments. While animal studies are precisely controlled, drug conditioning in humans is highly variably across individuals and drugs of abuse. Human addicts may use drugs in numerous environments under various circumstances. Similarly, over the course of drug use, human addicts might be exposed to thousands of learning trials, whereas animal studies involve comparatively limited drug-cue pairings. In addition, given the extensive amount of learning a typical addict engages in, the number of extinction trials conducted in treatment are likely to be relatively few. Although these factors most probably affect the magnitude and generality of conditioned effects in humans, they do not necessarily obviate the insights that can be derived from animal learning research on the most salient threats to extinction training. Renewal, spontaneous recovery, reinstatement and cue selection each pose a strong challenge to the development and maintenance of new learning for both human and animal subjects. Unfortunately, cue-exposure treatments have clearly not been designed to protect human addicts against these phenomena.

As noted in this review, animal extinction studies have revealed that the probability of an animal behaving according to what was learned during extinction rather than conditioning is largely context-dependent (Bouton 1994). Most critically, extinction learning will not generalize across contexts if extinction training takes place in only one context (Gunther *et al.* 1998; Chelonis *et al.* 1999). In nearly every case, cue-exposure treatment has been conducted in one room across all treatment sessions. These procedures reduce extinction generalizability, thereby increasing the likelihood that an addict confronted with extinguished drug cues in various contexts post-treatment will behave according to original learning (i.e. use drugs). The use of only one extinction context also increases the probability that the addict will associate unique attributes of the therapy context with extinction. When those attributes are absent in post-treatment environments, the addict is less likely to activate learning acquired during extinction.

The typical spacing of cue exposure within and between treatment sessions also increases the possibility of post-treatment spontaneous recovery. Animal research indicates that spontaneous recovery can be attenuated by fully extinguishing cues through multiple exposures, and by allowing for in-session and between-session recovery followed by additional extinction training. Cue-exposure treatments typically involved presenting a target cue only once, thereby preventing complete extinction. Moreover, when the same cue was presented several times, exposures were usually closely spaced, preventing within-session recovery before exposure continued. Although cue-exposure treatment sessions were typically separated by a day or several days, by and large the spacing between sessions was not tied to the addicts' responsivity. That is, researchers failed to utilized response-based information in order to systematically determine the amount of time before a cue should have been presented in a following session or decide when presentations could cease due to complete extinction.

This review presents numerous circumstances that threaten the likelihood of an addict behaving according to extinction rather than conditioning learning. Undoubtedly, the largest threat to the probability of an addict behaving according to extinction learning is the failure to expose addicts to the drug administration routine during extinction training. Without the experience of unreinforced drug-taking, addicts never learn an

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alternative association with drug administration, namely that it does not lead to drug effects. Therefore, following treatment, when confronted with proximal drug cues and the opportunity to engage in actual drug use, addicts have only the excitatory associations acquired over a long history of drug administration to guide their behavior. Breaking the association between drugs and reinforcing drug effects remains a challenge to addiction treatments. Therefore, unreinforced drug administration might prove to be cue-exposure treatment's greatest asset. However, with the exception of one limited investigation (O'Brien *et al*. 1979), cue exposure treatments have yet to use this potentially potent technique.

In addition to fundamental changes in the design of cue-exposure treatment, attempts to increase cue-exposure's efficacy must be guided by basic human research. This review has revealed the need for human research investigating the impact of changes in various contextual attributes (e.g. lighting, smell) on extinction learning, as well as the effect of personalized contextual alterations on extinction generalization. Research must also identify the number of contexts needed to substantially decrease renewal. It might be the case that the number of contexts needed to attenuate renewal varies across drugs of abuse. For example, smokers probably use nicotine in a greater number of contexts than opiate addicts use heroin. Therefore, a larger number and variety of extinction contexts may be needed to attenuate renewal in smokers.

Research is also needed to determine the temporal and spatial parameters of cue-exposure treatment most likely to attenuate spontaneous recovery. Researchers need to identify the time interval at which spontaneous recovery peaks in humans, thereby allowing informed decisions to be made regarding the timing of re-exposure to cues and the need for additional extinction. These decisions must also be made in consideration of addicts' responsivity to target drug cues. Therefore, extinction learning must be tracked, and the best methods of doing so can be revealed through cue-reactivity research. Specifically, cue-reactivity work investigating the value of different response measures (e.g. self-report, physiological, behavioral) for tracking extinction learning and between treatment sessions needs to be conducted. Finally, researchers also need to determine effective ways of preparing addicts for the potential discomfort cue-exposure treatment might invoke.

This review has focused on specific techniques for systematically improving cue-exposure's effectiveness as an addiction treatment. In addition to implementing new treatment strategies and conducting basic human research, efforts to improve cue-exposure's effectiveness must be guided by findings from ongoing studies in animal extinction. Many of the treatment ideas presented in this review were generated in consideration of work published within the past few years. As animal extinction research evolves, it will continue to provide critical information directly applicable to cue-exposure treatment. Indeed, it is rare to find any area of clinical endeavor that can take such immediate advantage of basic findings from the animal laboratory. Cue-exposure researchers should be prepared to exploit the wealth of animal extinction research that can directly guide their attempts to extinguish addictive behavior.

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